

SULPHAMOYL UREA DERIVATIVES CONTAINING ALKYL-OXACYCLOALKYL MOIETY AND USES THEREOF

RELATED APPLICATIONS

[001] This application claims priority to U.S. Provisional Application No. 63/074,521, filed September 4, 2020, the entire contents of which is incorporated herein by reference.

FIELD OF THE DISCLOSURE

[002] The present disclosure concerns sulphamoyl urea derivatives containing alkyl-oxacycloalkyl moiety, prodrugs, and pharmaceutically acceptable salts thereof, which may possess inflammasome inhibitory activity and are accordingly useful in methods of treatment of the human or animal body. The present disclosure also relates to processes for the preparation of these compounds, to pharmaceutical compositions comprising them and to their use in the treatment of disorders in which inflammasome activity is implicated, such as inflammatory, autoinflammatory and autoimmune and oncological diseases.

BACKGROUND

[003] Autoimmune diseases are associated with the overproduction of proinflammatory factors. One of them is interleukin-1 (IL-1), produced by activated macrophages, monocytes, fibroblasts, and other components of the innate immune system like dendritic cells. IL-1 is involved in a variety of cellular activities, including cell proliferation, differentiation and apoptosis (Masters, S. L., et. al., Annu. Rev. Immunol. 2009, 27:621–68).

[004] In humans, 22 NLR proteins are divided into four NLR subfamilies according to their N-terminal domains. NLRA contains a CARD-AT domain, NLRB (NAIP) contains a BIR domain, NLRC (including NOD1 and NOD2) contains a CARD domain, and NLRP contains a pyrin domain. Multiple NLR family members are associated with inflammasome formation.

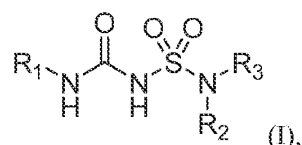
[005] Although inflammasome activation appears to have evolved as an important component of host immunity to pathogens, the NLRP3 inflammasome is unique in its ability activate in response to endogenous sterile danger signals. Many such sterile signals have been elucidated, and their formation is associated with specific disease states. For example, uric acid crystals found in gout patients are effective triggers of NLRP3 activation. Similarly, cholesterol crystals found

in atherosclerotic patients can also promote NLRP3 activation. Recognition of the role of sterile danger signals as NLRP3 activators led to IL-1 and IL-18 being implicated in a diverse range of pathophysiological indications including metabolic, physiologic, inflammatory, hematologic and immunologic disorders.

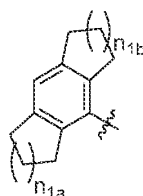
[006] The disclosure arises from a need to provide further compounds for the specific modulation of NLRP3-dependent cellular processes. In particular, compounds with improved physicochemical, pharmacological and pharmaceutical properties to existing compounds are desirable.

SUMMARY

[007] In some aspects, the present disclosure relates to a compound of Formula (I):



or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein:



R_1 is --- , wherein n_{1a} and n_{1b} each independently are 0 or 1;

R_2 is $\text{---}(\text{CH}_2)_{n_2}\text{---R}_{2S}$, wherein n_2 is 1 or 2;

R_{2S} is 4- to 8-membered heterocycloalkyl in which at least one heteroatom is O, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with one or more R_{2SS} ;

each R_{2SS} independently is $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ haloalkyl, halo, -CN , -OH , $\text{-O}(\text{C}_1\text{-C}_6 \text{ alkyl})$, -NH_2 , $\text{-NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$, $\text{-N}(\text{C}_1\text{-C}_6 \text{ alkyl})_2$, or oxo;

R_3 is 5- or 6-membered heteroaryl optionally substituted with one or more R_{3S} ; and

each R_{3S} independently is halo, $\text{C}_1\text{-C}_6$ alkyl, or $\text{C}_1\text{-C}_6$ haloalkyl.

[008] In some aspects, the present disclosure provides a compound obtainable by, or obtained by, a method for preparing a compound as described herein (e.g., a method comprising one or more steps described in Schemes 1 and 2).

[009] In some embodiments, the present disclosure provides a pharmaceutical composition comprising a compound described herein and one or more pharmaceutically acceptable carriers or excipients.

[010] In some aspects, the present disclosure provides an intermediate as described herein, being suitable for use in a method for preparing a compound as described herein (e.g., the intermediate is selected from the intermediates described in Examples 1-12).

[011] In some aspects, the present disclosure provides a method of inhibiting inflammasome (e.g., the NLRP3 inflammasome) activity (e.g., *in vitro* or *in vivo*), comprising contacting a cell with an effective amount of a compound of the present disclosure.

[012] In some aspects, the present disclosure provides a method of treating or preventing a disease or disorder disclosed herein in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure or a pharmaceutical composition of the present disclosure.

[013] In some aspects, the present disclosure provides a compound of the present disclosure for use in inhibiting inflammasome (e.g., the NLRP3 inflammasome) activity (e.g., *in vitro* or *in vivo*).

[014] In some aspects, the present disclosure provides a compound of the present disclosure or a pharmaceutically acceptable salt thereof for use in treating or preventing a disease or disorder disclosed herein.

[015] In some aspects, the present disclosure provides use of a compound of the present disclosure in the manufacture of a medicament for inhibiting inflammasome (e.g., the NLRP3 inflammasome) activity (e.g., *in vitro* or *in vivo*).

[016] In some aspects, the present disclosure provides use of a compound of the present disclosure in the manufacture of a medicament for treating or preventing a disease or disorder disclosed herein.

[017] In some aspects, the present disclosure provides a method of preparing a compound of the present disclosure.

[018] In some aspects, the present disclosure provides a method of a compound, comprising one or more steps described herein.

[019] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. In the specification, the singular forms also include the plural unless the context clearly

dictates otherwise. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods and materials are described below. All publications, patent applications, patents and other references mentioned herein are incorporated by reference. The references cited herein are not admitted to be prior art to the claimed invention. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods and examples are illustrative only and are not intended to be limiting. In the case of conflict between the chemical structures and names of the compounds disclosed herein, the chemical structures will control.

[020] Other features and advantages of the disclosure will be apparent from the following detailed description and claims.

DETAILED DESCRIPTION

[021] Autoimmune diseases are associated with the overproduction of proinflammatory factors. One of them is interleukin-1 (IL-1), produced by activated macrophages, monocytes, fibroblasts, and other components of the innate immune system like dendritic cells, involved in a variety of cellular activities, including cell proliferation, differentiation and apoptosis (Masters, S. L. et al., *Annu. Rev. Immunol.* 2009, 27:621–68).

[022] Cytokines from the IL-1 family are highly active and, as important mediators of inflammation, primarily associated with acute and chronic inflammation (Sims, J. et al. *Nature Reviews Immunology* 10, 89-102 (February 2010)). The overproduction of IL-1 is considered to be a mediator of some autoimmune and autoinflammatory diseases. Autoinflammatory diseases are characterised by recurrent and unprovoked inflammation in the absence of autoantibodies, infection, or antigen-specific T lymphocytes.

[023] Proinflammatory cytokines of the IL-1 superfamily include IL-1 α , IL-1 β , IL-18, and IL-36 α , β , λ and are produced in response to pathogens and other cellular stressors as part of a host innate immune response. Unlike many other secreted cytokines, which are processed and released via the standard cellular secretory apparatus consisting of the endoplasmic reticulum and Golgi apparatus, IL-1 family members lack leader sequences required for endoplasmic reticulum entry and thus are retained intracellularly following translation. In addition, IL-1 β , IL-18, and IL-36 α , β , λ are synthesised as procytokines that require proteolytic activation to become optimal ligands for binding to their cognate receptors on target cells.

[024] In the case of IL-1 α , IL-1 β and IL-18, it is now appreciated that a multimeric protein complex known as an inflammasome is responsible for activating the proforms of IL-1 β and IL-18 and for release of these cytokines extracellularly. An inflammasome complex typically consists of a sensor molecule, such as an NLR (Nucleotide-Oligomerisation Domain (NOD)-like receptor), an adaptor molecule ASC (Apoptosis-associated speck-like protein containing a CARD (Caspase Recruitment Domain)) and procaspase-1. In response to a variety of “danger signals”, including pathogen-associated molecule patterns (PAMPs) and danger associated molecular patterns (DAMPs), subunits of an inflammasome oligomerise to form a supramolecular structure within the cell. PAMPs include molecules such as peptidoglycan, viral DNA or RNA and bacterial DNA or RNA. DAMPs, on the other hand, consist of a wide range of endogenous or exogenous sterile triggers including monosodium urate crystals, silica, alum, asbestos, fatty acids, ceramides, cholesterol crystals and aggregates of beta-amyloid peptide. Assembly of an inflammasome platform facilitates autocatalysis of procaspase-1 yielding a highly active cysteine protease responsible for activation and release of pro-IL-1 β and pro-IL-18. Thus, release of these highly inflammatory cytokines is achieved only in response to inflammasome sensors detecting and responding to specific molecular danger signals.

[025] In humans, 22 NLR proteins are divided into four NLR subfamilies according to their N-terminal domains. NLRA contains a CARD-AT domain, NLRB (NAIP) contains a BIR domain, NLRC (including NOD1 and NOD2) contains a CARD domain, and NLRP contains a pyrin domain. Multiple NLR family members are associated with inflammasome formation including NLRP1, NLRP3, NLRP6, NLRP7, NLRP12 and NLRC4 (IPAF).

[026] Two other structurally distinct inflammasome structures containing a PYHIN domain (pyrin and HIN domain containing protein) namely Absent in Melanoma 2 (AIM2) and IFN λ -inducible protein 16 (IFI16) (Latz et al., Nat Rev Immunol 2013 13(6) 397-311) serve as intracellular DNA sensors. Pyrin (encoded by the MEFV gene) represents another type of inflammasome platform associated with proIL-1 β activation (Chae et al., Immunity 34, 755-768, 2011).

[027] Requiring assembly of an inflammasome platform to achieve activation and release of IL-1 β and IL-18 from monocytes and macrophages ensures their production is carefully orchestrated via a 2-step process. First, the cell must encounter a priming ligand (such as the TLR4 receptor ligand LPS, or an inflammatory cytokine such as TNF α) which leads to NF κ B dependent

transcription of NLRP3, pro-IL-1 β and pro-IL-18. The newly translated procytokines remain intracellular and inactive unless producing cells encounter a second signal leading to activation of an inflammasome scaffold and maturation of procaspase-1.

[028] In addition to proteolytic activation of pro-IL-1 β and pro-IL-18, active caspase-1 also triggers a form of inflammatory cell death known as pyroptosis through cleavage of gasdermin-D. Pyroptosis allows the mature forms of IL-1 β and IL-18 to be externalised along with release of alarmin molecules (compounds that promote inflammation and activate innate and adaptive immunity) such as high mobility group box 1 protein (HMGB1), IL-33, and IL-1 α .

[029] Although inflammasome activation appears to have evolved as an important component of host immunity to pathogens, the NLRP3 inflammasome is unique in its ability activate in response to endogenous and exogenous sterile danger signals. Many such sterile signals have been elucidated, and their formation is associated with specific disease states. For example, uric acid crystals found in gout patients are effective triggers of NLRP3 activation. Similarly, cholesterol crystals found in atherosclerotic patients can also promote NLRP3 activation. Recognition of the role of sterile danger signals as NLRP3 activators led to IL-1 β and IL-18 being implicated in a diverse range of pathophysiological indications including metabolic, physiologic, inflammatory, haematologic and immunologic disorders.

[030] A link to human disease is best exemplified by discovery that mutations in the NLRP3 gene which lead to gain-of-function confer a range of autoinflammatory conditions collectively known as cryopyrin-associated periodic syndromes (CAPS) including familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and Neonatal onset multisystem inflammatory disease (NOMID) (Hoffman et al., Nat Genet. 29(3) (2001) 301-305). Likewise, sterile mediator-induced activation of NLRP3 has been implicated in a wide range of disorders including joint degeneration (gout, rheumatoid arthritis, osteoarthritis), cardiometabolic (type 2 diabetes, atherosclerosis, hypertension), Central Nervous System (Alzheimer's Disease, Parkinson's disease, multiple sclerosis), gastrointestinal (Crohn's disease, ulcerative colitis), lung (chronic obstructive pulmonary disease (COPD), asthma, idiopathic pulmonary fibrosis) and liver (fibrosis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis (NASH)). It is further believed that NLRP3 activation promotes kidney inflammation and thus contributes to chronic kidney disease (CKD).

[031] Current treatment options for diseases where IL-1 is implicated as a contributor to pathogenesis include the IL-1 receptor antagonist anakinra, an Fc-containing fusion construct of the extracellular domains of the IL-1 receptor and IL-1 receptor accessory protein (rilonacept) and the anti-IL-1 β monoclonal antibody canakinumab. For example, canakinumab is licensed for CAPS, Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), Familial Mediterranean Fever (FMF) and gout.

[032] Some small molecules have been reported to inhibit function of the NLRP3 inflammasome. Glyburide, for example, is a specific inhibitor of NLRP3 activation, albeit at micromolar concentrations which are unlikely attainable *in vivo*. Non-specific agents such as parthenolide, Bay 11-7082, and 3,4-methylenedioxy- β -nitrostyrene are reported to impair NLRP3 activation but are expected to possess limited therapeutic utility due to their sharing of a common structural feature consisting of an olefin activated by substitution with an electron withdrawing group; this can lead to undesirable formation of covalent adducts with protein-bearing thiol groups. A number of natural products, for example β -hydroxybutyrate, sulforaphane, quercetin, and salvianolic acid, also are reported to suppress NLRP3 activation. Likewise, numerous effectors/modulators of other molecular targets have been reported to impair NLRP3 activation including agonists of the G-protein coupled receptor TGR5, an inhibitor of sodium-glucose co-transport epigliflozin, the dopamine receptor antagonist A-68930, the serotonin reuptake inhibitor fluoxetine, fenamate non-steroidal anti-inflammatory drugs, and the β -adrenergic receptor blocker nebivolol. Utility of these molecules as therapeutics for the chronic treatment of NLRP3-dependent inflammatory disorders remains to be established. A series of sulphonylurea-containing molecules was previously identified as potent and selective inhibitors of post-translational processing of pro-IL-1 β (Perregaux et al., J Pharmacol. Exp. Ther. 299, 187-197, 2001). The exemplar molecule CP-456,773 from this work was characterised as a specific inhibitor of NLRP3 activation (Coll et al., Nat Med 21.3 (2015): 248-255.).

[033] The disclosure relates to compounds useful for the specific modulation of NLRP3-dependent cellular processes. In particular, compounds with improved physicochemical, pharmacological and pharmaceutical properties to existing NLRP3-modulating compounds are desired.

Definitions

[034] Unless otherwise stated, the following terms used in the specification and claims have the following meanings set out below.

[035] Without wishing to be limited by this statement, it is understood that, while various options for variables are described herein, the disclosure intends to encompass operable embodiments having combinations of the options. The disclosure may be interpreted as excluding the non-operable embodiments caused by certain combinations of the options.

[036] It is to be understood that a compound of the present disclosure may be depicted in a neutral form, a cationic form (e.g., carrying one or more positive charges), or an anionic form (e.g., carrying one or more negative charges), all of which are intended to be included in the scope of the present disclosure. For example, when a compound of the present disclosure is depicted in an anionic form, it should be understood that such depiction also refers to the various neutral forms, cationic forms, and anionic forms of the compound. For another example, when a compound the present disclosure is depicted in an anionic form, it should be understood that such depiction also refers to various salts (e.g., sodium salt) of the anionic form of the compound.

[037] A “therapeutically effective amount” means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The “therapeutically effective amount” will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

[038] As used herein, “alkyl”, “C₁, C₂, C₃, C₄, C₅ or C₆ alkyl” or “C₁-C₆ alkyl” is intended to include C₁, C₂, C₃, C₄, C₅ or C₆ straight chain (linear) saturated aliphatic hydrocarbon groups and C₃, C₄, C₅ or C₆ branched saturated aliphatic hydrocarbon groups. For example, C₁-C₆ alkyl is intends to include C₁, C₂, C₃, C₄, C₅ and C₆ alkyl groups. Examples of alkyl include, moieties having from one to six carbon atoms, such as, but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl or n-hexyl. In some embodiments, a straight chain or branched alkyl has six or fewer carbon atoms (e.g., C₁-C₆ for straight chain, C₃-C₆ for branched chain), and in another embodiment, a straight chain or branched alkyl has four or fewer carbon atoms.

[039] As used herein, the term “optionally substituted alkyl” refers to unsubstituted alkyl or alkyl having designated substituents replacing one or more hydrogen atoms on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl, alkenyl,

alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylaryl amino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphhydryl, alkylthio, arylthio, thiocarboxylate, sulphates, alkylsulphinyl, sulphonato, sulphamoyl, sulphonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[040] As used herein, the term “alkenyl” includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond. For example, the term “alkenyl” includes straight chain alkenyl groups (*e.g.*, ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl), and branched alkenyl groups. In certain embodiments, a straight chain or branched alkenyl group has six or fewer carbon atoms in its backbone (*e.g.*, C₂-C₆ for straight chain, C₃-C₆ for branched chain). The term “C₂-C₆” includes alkenyl groups containing two to six carbon atoms. The term “C₃-C₆” includes alkenyl groups containing three to six carbon atoms.

[041] As used herein, the term “optionally substituted alkenyl” refers to unsubstituted alkenyl or alkenyl having designated substituents replacing one or more hydrogen atoms on one or more hydrocarbon backbone carbon atoms. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylaryl amino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphhydryl, alkylthio, arylthio, thiocarboxylate, sulphates, alkylsulphinyl, sulphonato, sulphamoyl, sulphonamido, nitro, trifluoromethyl, cyano, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[042] As used herein, the term “alkynyl” includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond. For example, “alkynyl” includes straight chain alkynyl groups (*e.g.*, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl), and branched alkynyl groups.

In certain embodiments, a straight chain or branched alkynyl group has six or fewer carbon atoms in its backbone (e.g., C₂-C₆ for straight chain, C₃-C₆ for branched chain). The term "C₂-C₆" includes alkynyl groups containing two to six carbon atoms. The term "C₃-C₆" includes alkynyl groups containing three to six carbon atoms. As used herein, "C₂-C₆ alkenylene linker" or "C₂-C₆ alkynylene linker" is intended to include C₂, C₃, C₄, C₅ or C₆ chain (linear or branched) divalent unsaturated aliphatic hydrocarbon groups. For example, C₂-C₆ alkenylene linker is intended to include C₂, C₃, C₄, C₅ and C₆ alkenylene linker groups.

[043] As used herein, the term "optionally substituted alkynyl" refers to unsubstituted alkynyl or alkynyl having designated substituents replacing one or more hydrogen atoms on one or more hydrocarbon backbone carbon atoms. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphhydryl, alkylthio, arylthio, thiocarboxylate, alkylsulphinyl, sulphonato, sulphamoyl, sulphonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[044] Other optionally substituted moieties (such as optionally substituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl) include both the unsubstituted moieties and the moieties having one or more of the designated substituents. For example, substituted heterocycloalkyl includes those substituted with one or more alkyl groups, such as 2,2,6,6-tetramethyl-piperidinyl and 2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridinyl.

[045] As used herein, the term "cycloalkyl" refers to a saturated or partially unsaturated hydrocarbon monocyclic or polycyclic (e.g., fused, bridged, or spiro rings) system having 3 to 30 carbon atoms (e.g., C₃-C₁₂, C₃-C₁₀, or C₃-C₈). Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, 1,2,3,4-tetrahydronaphthalenyl, and adamantyl. In the case of polycyclic cycloalkyl, only one of the rings in the cycloalkyl needs to be non-aromatic.

[046] As used herein, the term "heterocycloalkyl" refers to a saturated or partially unsaturated 3-8 membered monocyclic, 7-12 membered bicyclic (fused, bridged, or spiro rings), or 11-14

membered tricyclic ring system (fused, bridged, or spiro rings) having one or more heteroatoms (such as O, N, S, P, or Se), e.g., 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, or e.g., 1, 2, 3, 4, 5, or 6 heteroatoms, independently selected from the group consisting of nitrogen, oxygen and sulphur, unless specified otherwise. Examples of heterocycloalkyl groups include, but are not limited to, piperidinyl, piperazinyl, pyrrolidinyl, dioxanyl, tetrahydrofuranyl, isoindolinyl, indolinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, oxiranyl, azetidiny, oxetanyl, thietanyl, 1,2,3,6-tetrahydropyridinyl, tetrahydropyranyl, dihydropyranyl, pyranyl, morpholinyl, tetrahydrothiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, 1,4-dioxo-8-azaspiro[4.5]decanyl, 1,4-dioxaspiro[4.5]decanyl, 1-oxaspiro[4.5]decanyl, 1-azaspiro[4.5]decanyl, 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-yl, 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-yl, 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-yl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[3.1.0]hexan-3-yl, 1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazolyl, 3,4,5,6,7,8-hexahydropyrido[4,3-d]pyrimidinyl, 4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridinyl, 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidinyl, 2-azaspiro[3.3]heptanyl, 2-methyl-2-azaspiro[3.3]heptanyl, 2-azaspiro[3.5]nonanyl, 2-methyl-2-azaspiro[3.5]nonanyl, 2-azaspiro[4.5]decanyl, 2-methyl-2-azaspiro[4.5]decanyl, 2-oxa-azaspiro[3.4]octanyl, 2-oxa-azaspiro[3.4]octan-6-yl, and the like. In the case of multicyclic heterocycloalkyl, only one of the rings in the heterocycloalkyl needs to be non-aromatic (e.g., 4,5,6,7-tetrahydrobenzo[c]isoxazolyl).

[047] As used herein, the term “aryl” includes groups with aromaticity, including “conjugated,” or multicyclic systems with one or more aromatic rings and do not contain any heteroatom in the ring structure. The term aryl includes both monovalent species and divalent species. Examples of aryl groups include, but are not limited to, phenyl, biphenyl, naphthyl and the like. Conveniently, an aryl is phenyl.

[048] As used herein, the term “heteroaryl” is intended to include a stable 5-, 6-, or 7-membered monocyclic or 7-, 8-, 9-, 10-, 11- or 12-membered bicyclic aromatic heterocyclic ring which consists of carbon atoms and one or more heteroatoms, e.g., 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, or e.g., 1, 2, 3, 4, 5, or 6 heteroatoms, independently selected from the group consisting of nitrogen, oxygen and sulphur. The nitrogen atom may be substituted or unsubstituted (i.e., N or NR wherein R is H or other substituents, as defined). The nitrogen and sulphur

heteroatoms may optionally be oxidised (*i.e.*, $N \rightarrow O$ and $S(O)_p$, where $p = 1$ or 2). It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1. Examples of heteroaryl groups include pyrrole, furan, thiophene, thiazole, isothiazole, imidazole, triazole, tetrazole, pyrazole, oxazole, isoxazole, pyridine, pyrazine, pyridazine, pyrimidine, and the like. Heteroaryl groups can also be fused or bridged with alicyclic or heterocyclic rings, which are not aromatic so as to form a multicyclic system (*e.g.*, 4,5,6,7-tetrahydrobenzo[c]isoxazolyl).

[049] Furthermore, the terms “aryl” and “heteroaryl” include multicyclic aryl and heteroaryl groups, *e.g.*, tricyclic, bicyclic, *e.g.*, naphthalene, benzoxazole, benzodioxazole, benzothiazole, benzoimidazole, benzothiophene, quinoline, isoquinoline, naphthyridine, indole, benzofuran, purine, deazapurine, indolizine.

[050] The cycloalkyl, heterocycloalkyl, aryl, or heteroaryl ring can be substituted at one or more ring positions (*e.g.*, the ring-forming carbon or heteroatom such as N) with such substituents as described above, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy, carboxylate, alkylcarbonyl, alkylaminocarbonyl, aralkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonate, phosphinate, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphhydryl, alkylthio, arylthio, thiocarboxylate, sulphates, alkylsulphinyl, sulphonate, sulphamoyl, sulphonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl and heteroaryl groups can also be fused or bridged with alicyclic or heterocyclic rings, which are not aromatic so as to form a multicyclic system (*e.g.*, tetralin, methylenedioxyphenyl such as benzo[d][1,3]dioxole-5-yl).

As used herein, the term “substituted,” means that any one or more hydrogen atoms on the designated atom is replaced with a selection from the indicated groups, provided that the designated atom’s normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is oxo or keto (*i.e.*, $=O$), then 2 hydrogen atoms on the atom are replaced. Keto substituents are not present on aromatic moieties. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (*e.g.*, $C=C$, $C=N$ or $N=N$). “Stable compound” and “stable structure” are meant to indicate a compound that is

sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

[051] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom in the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such formula. Combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

[052] When any variable (*e.g.*, R) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R moieties, then the group may optionally be substituted with up to two R moieties and R at each occurrence is selected independently from the definition of R. Also, combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

[053] As used herein, the term “hydroxy” or “hydroxyl” includes groups with an -OH or -O⁻.

[054] As used herein, the term “halo” or “halogen” refers to fluoro, chloro, bromo and iodo.

[055] The term “haloalkyl” or “haloalkoxy” refers to an alkyl or alkoxy substituted with one or more halogen atoms.

[056] As used herein, the term “optionally substituted haloalkyl” refers to unsubstituted haloalkyl having designated substituents replacing one or more hydrogen atoms on one or more hydrocarbon backbone carbon atoms. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonate, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylaryl amino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphhydryl, alkylthio, arylthio, thiocarboxylate, sulphates, alkylsulphinyl, sulphonate, sulphamoyl, sulphonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[057] As used herein, the term “alkoxy” or “alkoxyl” includes substituted and unsubstituted alkyl, alkenyl and alkynyl groups covalently linked to an oxygen atom. Examples of alkoxy groups

or alkoxyl radicals include, but are not limited to, methoxy, ethoxy, isopropoxy, propoxy, butoxy and pentoxy groups. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphhydryl, alkylthio, arylthio, thiocarboxylate, sulphates, alkylsulphinyl, sulphonato, sulphamoyl, sulphonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy and trichloromethoxy.

[058] As used herein, the expressions “one or more of A, B, or C,” “one or more A, B, or C,” “one or more of A, B, and C,” “one or more A, B, and C,” “selected from the group consisting of A, B, and C”, “selected from A, B, and C”, and the like are used interchangeably and all refer to a selection from a group consisting of A, B, and/or C, i.e., one or more As, one or more Bs, one or more Cs, or any combination thereof, unless indicated otherwise.

[059] As used herein “Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV 2)” refers to the coronavirus that caused the 2019 novel coronavirus disease (COVID-19). COVID-19 was first identified in 2019 in Wuhan, China, and has resulted in an ongoing global pandemic. As of August 2020, more than 25 million cases have been reported globally, resulting in an estimated 848,000 deaths. Common symptoms of COVID-19 include fever, cough, fatigue, shortness of breath, and loss of smell and taste. While many people have mild symptoms, some people develop acute respiratory distress syndrome, possibly caused by cytokine release syndrome (CRS), multi-organ failure, septic shock and blood clots. Time from exposure to the virus to symptom onset is typically around 5 days, but may range from 2 to 14 days. In some embodiments, SARS-CoV 2 refers to a mutation of the coronavirus that caused the 2019 novel coronavirus disease (COVID-19).

[060] In some embodiments, the coronavirus can be SARS-CoV (*i.e.* SARS), SARS-CoV-2, MERS-CoV (*i.e.* MERS), or a mutant and/or variant thereof. In some embodiments, the subject

has a disease of pathology associated with MERS and/or its variants. In some embodiments, the subject has a disease or pathology associated with SARS and/or its variants. In some embodiments, the subject has a disease or pathology associated with SARS-CoV-2 and/or its variants. “Variants” refers to genetic variants of a coronavirus, such that novel genetic mutations have occurred in the variant in relation to one or more known strains of the coronavirus. Mutations (*e.g.* substitutions or deletions) can be to any nucleotide in the genome of the coronavirus. The variants can be variants of interest, variants of concern, or variants of high consequence. For example the B.1.1.7 (Alpha), B.1.351 (Beta), B.1.617 (Delta), and P.1 (Gamma), B.1.526 (Iota), B.1.427 (Epsilon), B.1.429 (Epsilon), B.1.1.7 (Alpha), P.2 (Zeta), and their lineages are classified as variants of SARS-CoV-2. It is understood that new variants of coronavirus with novel mutations or sets of mutations can arise, and these are also covered by the term “coronavirus” as referred to herein.

[061] As used herein “cytokine release syndrome (CRS)” refers to a systemic inflammatory response that can be triggered by a variety of factors, including but not limited to drugs, infections such as SARS-CoV 2, and immunotherapies such as chimeric antigen receptor T cell (CAR-T) therapies. In CRS, large numbers of immune cells (*e.g.* T cells) are activated and release inflammatory cytokines, which in turn activate additional immune cells. Symptoms include fever, fatigue, loss of appetite, muscle and joint pain, nausea, vomiting, diarrhea, rashes, respiratory insufficiency, low blood pressure, seizures, headache and confusion. CRS may respond to IL-6 receptor inhibition, and high doses of steroids.

[062] As used herein, “adoptive cell therapy” refers to a form of treatment that uses immune cells to treat diseases such as cancer. Immune cells, for example T cells are collected from the subject or another source, grown in large numbers, and implanted into the subject to help the immune system fight the disease. Types of adoptive cell therapy include chimeric antigen receptor T cell (CAR-T) therapy, tumor infiltrating lymphocyte (TIL) therapy, and T cell receptor T cell (TCR-T) therapy.

[063] The term “chimeric antigen receptors (CARs),” as used herein, may refer to artificial T-cell receptors, chimeric T-cell receptors, or chimeric immunoreceptors, for example, and encompass engineered receptors that graft an artificial specificity onto a particular immune effector cell. CARs may be employed to impart the specificity of a monoclonal antibody onto a T cell, thereby allowing a large number of specific T cells to be generated, for example, for use in

adoptive cell therapy. For example, CARs may direct specificity of the cell expressing the CAR to a tumor associated antigen. In some embodiments, CARs comprise an intracellular activation domain, a transmembrane domain, and an extracellular domain comprising an antigen binding domain, and optionally an extracellular hinge. The antigen binding domain can be any antigen binding domain known in the art, including antigen binding domains derived from antibodies, Fab, F(ab')₂, nanobodies, single domain antigen binding domains, scFv, VHH, and the like. In particular aspects, CARs comprise fusions of single-chain variable fragments (scFv) derived from monoclonal antibodies, fused to a CD3 transmembrane domain and endodomain. In certain cases, CARs comprise domains for additional co-stimulatory signaling, such as CD3, FcR, CD27, CD28, CD137, DAP10, and/or OX40.

[064] A "T cell receptor (TCR)" is a protein complex found on the surface of T cells, or T lymphocytes, that is responsible for recognizing fragments of antigen as peptides bound to major histocompatibility complex (MHC) molecules. T cell receptors can be engineered to express antigen binding domains specific to particular antigens, and used in the adoptive cell therapies described herein.

[065] It is to be understood that the present disclosure provides methods for the synthesis of the compounds of any of the Formulae described herein. The present disclosure also provides detailed methods for the synthesis of various disclosed compounds of the present disclosure according to the following schemes as well as those shown in the Examples.

[066] It is to be understood that, throughout the description, where compositions are described as having, including, or comprising specific components, it is contemplated that compositions also consist essentially of, or consist of, the recited components. Similarly, where methods or processes are described as having, including, or comprising specific process steps, the processes also consist essentially of, or consist of, the recited processing steps. Further, it should be understood that the order of steps or order for performing certain actions is immaterial so long as the invention remains operable. Moreover, two or more steps or actions can be conducted simultaneously.

[067] It is to be understood that the synthetic processes of the disclosure can tolerate a wide variety of functional groups, therefore various substituted starting materials can be used. The processes generally provide the desired final compound at or near the end of the overall process, although it may be desirable in certain instances to further convert the compound to a pharmaceutically acceptable salt thereof.

[068] It is to be understood that compounds of the present disclosure can be prepared in a variety of ways using commercially available starting materials, compounds known in the literature, or from readily prepared intermediates, by employing standard synthetic methods and procedures either known to those skilled in the art, or which will be apparent to the skilled artisan in light of the teachings herein. Standard synthetic methods and procedures for the preparation of organic molecules and functional group transformations and manipulations can be obtained from the relevant scientific literature or from standard textbooks in the field. Although not limited to any one or several sources, classic texts such as Smith, M. B., March, J., *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th edition, John Wiley & Sons: New York, 2001; Greene, T.W., Wuts, P.G. M., *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons: New York, 1999; R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995), incorporated by reference herein, are useful and recognised reference textbooks of organic synthesis known to those in the art.

[069] One of ordinary skill in the art will note that, during the reaction sequences and synthetic schemes described herein, the order of certain steps may be changed, such as the introduction and removal of protecting groups. One of ordinary skill in the art will recognise that certain groups may require protection from the reaction conditions via the use of protecting groups. Protecting groups may also be used to differentiate similar functional groups in molecules. A list of protecting groups and how to introduce and remove these groups can be found in Greene, T.W., Wuts, P.G. M., *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons: New York, 1999.

[070] It is to be understood that, unless otherwise stated, any description of a method of treatment includes use of the compounds to provide such treatment or prophylaxis as is described herein, as well as use of the compounds to prepare a medicament to treat or prevent such condition. The treatment includes treatment of human or non-human animals including rodents and other disease models.

[071] As used herein, the term "subject" includes human and non-human animals, as well as cell lines, cell cultures, tissues, and organs. In some embodiments, the subject is a mammal. The mammal can be *e.g.*, a human or appropriate non-human mammal, such as primate, mouse, rat,

dog, cat, cow, horse, goat, camel, sheep or a pig. The subject can also be a bird or fowl. In some embodiments, the subject is a human.

[072] As used herein, the term “subject in need thereof” refers to a subject having a disease or having an increased risk of developing the disease. A subject in need thereof can be one who has been previously diagnosed or identified as having a disease or disorder disclosed herein. A subject in need thereof can also be one who is suffering from a disease or disorder disclosed herein. Alternatively, a subject in need thereof can be one who has an increased risk of developing such disease or disorder relative to the population at large (i.e., a subject who is predisposed to developing such disorder relative to the population at large). A subject in need thereof can have a refractory or resistant a disease or disorder disclosed herein (i.e., a disease or disorder disclosed herein that does not respond or has not yet responded to treatment). The subject may be resistant at start of treatment or may become resistant during treatment. In some embodiments, the subject in need thereof received and failed all known effective therapies for a disease or disorder disclosed herein. In some embodiments, the subject in need thereof received at least one prior therapy.

[073] As used herein, the term “treating” or “treat” describes the management and care of a patient for the purpose of combating a disease, condition, or disorder and includes the administration of a compound of the present disclosure, or a pharmaceutically acceptable salt, polymorph or solvate thereof, to alleviate the symptoms or complications of a disease, condition or disorder, or to eliminate the disease, condition or disorder. The term “treat” can also include treatment of a cell *in vitro* or an animal model.

[074] It is to be understood that a compound of the present disclosure, or a pharmaceutically acceptable salt, polymorph or solvate thereof, can or may also be used to prevent a relevant disease, condition or disorder, or used to identify suitable candidates for such purposes.

[075] As used herein, the term “preventing,” “prevent,” or “protecting against” describes reducing or eliminating the onset of the symptoms or complications of such disease, condition or disorder.

[076] It is to be understood that one skilled in the art may refer to general reference texts for detailed descriptions of known techniques discussed herein or equivalent techniques. These texts include Ausubel *et al.*, *Current Protocols in Molecular Biology*, John Wiley and Sons, Inc. (2005); Sambrook *et al.*, *Molecular Cloning, A Laboratory Manual* (3rd edition), Cold Spring Harbor Press, Cold Spring Harbor, New York (2000); Coligan *et al.*, *Current Protocols in Immunology*,

John Wiley & Sons, N.Y.; Enna *et al.*, *Current Protocols in Pharmacology*, John Wiley & Sons, N.Y.; Fingl *et al.*, *The Pharmacological Basis of Therapeutics* (1975), *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, PA, 18th edition (1990). These texts can, of course, also be referred to in making or using an aspect of the disclosure.

[077] It is to be understood that the present disclosure also provides pharmaceutical compositions comprising any compound described herein in combination with at least one pharmaceutically acceptable excipient or carrier.

[078] As used herein, the term “pharmaceutical composition” is a formulation containing the compounds of the present disclosure in a form suitable for administration to a subject. In one embodiment, the pharmaceutical composition is in bulk or in unit dosage form. The unit dosage form is any of a variety of forms, including, for example, a capsule, an IV bag, a tablet, a single pump on an aerosol inhaler or a vial. The quantity of active ingredient (*e.g.*, a formulation of the disclosed compound or salt, hydrate, solvate or isomer thereof) in a unit dose of composition is an effective amount and is varied according to the particular treatment involved. One skilled in the art will appreciate that it is sometimes necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration. A variety of routes are contemplated, including oral, pulmonary, rectal, parenteral, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal, inhalational, buccal, sublingual, intrapleural, intrathecal, intranasal, and the like. Dosage forms for the topical or transdermal administration of a compound of this disclosure include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. In one embodiment, the active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that are required.

[079] As used herein, the term “pharmaceutically acceptable” refers to those compounds, anions, cations, materials, compositions, carriers, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[080] As used herein, the term “pharmaceutically acceptable excipient” means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use

as well as human pharmaceutical use. A “pharmaceutically acceptable excipient” as used in the specification and claims includes both one and more than one such excipient.

[081] It is to be understood that a pharmaceutical composition of the disclosure is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, ingestion), inhalation, transdermal (topical), and transmucosal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulphite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[082] It is to be understood that a compound or pharmaceutical composition of the disclosure can be administered to a subject in many of the well-known methods currently used for chemotherapeutic treatment. For example, a compound of the disclosure may be injected into the blood stream or body cavities or taken orally or applied through the skin with patches. The dose chosen should be sufficient to constitute effective treatment but not so high as to cause unacceptable side effects. The state of the disease condition (*e.g.*, a disease or disorder disclosed herein) and the health of the patient should preferably be closely monitored during and for a reasonable period after treatment.

[083] As used herein, the term “therapeutically effective amount”, refers to an amount of a pharmaceutical agent to treat, ameliorate, or prevent an identified disease or condition, or to exhibit a detectable therapeutic or inhibitory effect. The effect can be detected by any assay method known in the art. The precise effective amount for a subject will depend upon the subject’s body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Therapeutically effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician.

[084] It is to be understood that, for any compound, the therapeutically effective amount can be estimated initially either in cell culture assays, *e.g.*, of neoplastic cells, or in animal models, usually

rats, mice, rabbits, dogs, or pigs. The animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans. Therapeutic/prophylactic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, ED₅₀ (the dose therapeutically effective in 50% of the population) and LD₅₀ (the dose lethal to 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index, and it can be expressed as the ratio, LD₅₀/ED₅₀. Pharmaceutical compositions that exhibit large therapeutic indices are preferred. The dosage may vary within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

[085] Dosage and administration are adjusted to provide sufficient levels of the active agent(s) or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

[086] The pharmaceutical compositions containing active compounds of the present disclosure may be manufactured in a manner that is generally known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilising processes. Pharmaceutical compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and/or auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Of course, the appropriate formulation is dependent upon the route of administration chosen.

[087] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and

storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol and sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[088] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilisation. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[089] Oral compositions generally include an inert diluent or an edible pharmaceutically acceptable carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a

sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[090] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser, which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebuliser.

[091] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[092] The active compounds can be prepared with pharmaceutically acceptable carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[093] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the disclosure are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved.

[094] In therapeutic applications, the dosages of the pharmaceutical compositions used in accordance with the disclosure vary depending on the agent, the age, weight, and clinical condition

of the recipient patient, and the experience and judgment of the clinician or practitioner administering the therapy, among other factors affecting the selected dosage. Generally, the dose should be sufficient to result in slowing, and preferably regressing, the symptoms of the disease or disorder disclosed herein and also preferably causing complete regression of the disease or disorder. Dosages can range from about 0.01 mg/kg per day to about 5000 mg/kg per day. In preferred aspects, dosages can range from about 1 mg/kg per day to about 1000 mg/kg per day. In an aspect, the dose will be in the range of about 0.1 mg/day to about 50 g/day; about 0.1 mg/day to about 25 g/day; about 0.1 mg/day to about 10 g/day; about 0.1 mg to about 3 g/day; or about 0.1 mg to about 1 g/day, in single, divided, or continuous doses (which dose may be adjusted for the patient's weight in kg, body surface area in m², and age in years). An effective amount of a pharmaceutical agent is that which provides an objectively identifiable improvement as noted by the clinician or other qualified observer. Improvement in survival and growth indicates regression. As used herein, the term "dosage effective manner" refers to amount of an active compound to produce the desired biological effect in a subject or cell.

[095] It is to be understood that the pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[096] It is to be understood that, for the compounds of the present disclosure being capable of further forming salts, all of these forms are also contemplated within the scope of the claimed disclosure.

[097] As used herein, the term "pharmaceutically acceptable salts" refer to derivatives of the compounds of the present disclosure wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulphonic, acetic, ascorbic, benzene sulphonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulphonic, 1,2-ethane sulphonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic,

lactobionic, lauryl sulphonic, maleic, malic, mandelic, methane sulphonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, subacetic, succinic, sulphamic, sulphanilic, sulphuric, tannic, tartaric, toluene sulphonic, and the commonly occurring amine acids, *e.g.*, glycine, alanine, phenylalanine, arginine, etc.

[098] In some embodiments, the pharmaceutically acceptable salt is a sodium salt, a potassium salt, a calcium salt, a magnesium salt, a diethylamine salt, a choline salt, a meglumine salt, a benzathine salt, a tromethamine salt, an ammonia salt, an arginine salt, or a lysine salt.

[099] Other examples of pharmaceutically acceptable salts include hexanoic acid, cyclopentane propionic acid, pyruvic acid, malonic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, 4-chlorobenzenesulphonic acid, 2-naphthalenesulphonic acid, 4-toluenesulphonic acid, camphorsulphonic acid, 4-methylbicyclo-[2.2.2]-oct-2-ene-1-carboxylic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, muconic acid, and the like. The present disclosure also encompasses salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. In the salt form, it is understood that the ratio of the compound to the cation or anion of the salt can be 1:1, or any ratio other than 1:1, *e.g.*, 3:1, 2:1, 1:2, or 1:3.

[0100] It is to be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same salt.

[0101] The compounds, or pharmaceutically acceptable salts thereof, are administered orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperitoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally and parenterally. In one embodiment, the compound is administered orally. One skilled in the art will recognise the advantages of certain routes of administration.

[0102] The dosage regimen utilising the compounds is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

[0103] Techniques for formulation and administration of the disclosed compounds of the disclosure can be found in *Remington: the Science and Practice of Pharmacy*, 19th edition, Mack Publishing Co., Easton, PA (1995). In an embodiment, the compounds described herein, and the pharmaceutically acceptable salts thereof, are used in pharmaceutical preparations in combination with a pharmaceutically acceptable carrier or diluent. Suitable pharmaceutically acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The compounds will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described herein.

[0104] All percentages and ratios used herein, unless otherwise indicated, are by weight. Other features and advantages of the present disclosure are apparent from the different examples. The provided examples illustrate different components and methodology useful in practicing the present disclosure. The examples do not limit the claimed disclosure. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present disclosure.

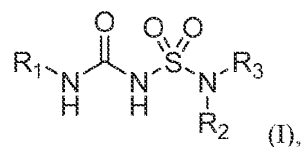
[0105] In the synthetic schemes described herein, compounds may be drawn with one particular configuration for simplicity. Such particular configurations are not to be construed as limiting the disclosure to one or another isomer, tautomer, regioisomer or stereoisomer, nor does it exclude mixtures of isomers, tautomers, regioisomers or stereoisomers; however, it will be understood that a given isomer, tautomer, regioisomer or stereoisomer may have a higher level of activity than another isomer, tautomer, regioisomer or stereoisomer.

[0106] All publications and patent documents cited herein are incorporated herein by reference as if each such publication or document was specifically and individually indicated to be incorporated herein by reference. Citation of publications and patent documents is not intended as an admission that any is pertinent prior art, nor does it constitute any admission as to the contents or date of the same. The invention having now been described by way of written description, those of skill in the art will recognize that the invention can be practiced in a variety of embodiments and that the foregoing description and examples below are for purposes of illustration and not limitation of the claims that follow.

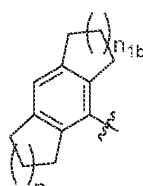
[0107] As used herein, the phrase “compound of the disclosure” refers to those compounds which are disclosed herein, both generically and specifically.

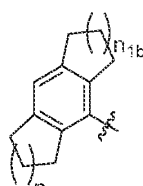
Compounds of the Present Disclosure

[0108] In some aspects, the present disclosure relates to a compound of Formula (I):



or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein:



R_1 is , wherein n_{1a} and n_{1b} each independently are 0 or 1;

R_2 is $-(\text{CH}_2)_{n_2}\text{-R}_{2S}$, wherein n_2 is 1 or 2;

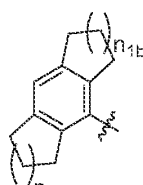
R_{2S} is 4- to 8-membered heterocycloalkyl in which at least one heteroatom is O, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with one or more R_{2SS} ;

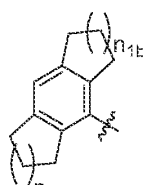
each R_{2SS} independently is $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ haloalkyl, halo, $-\text{CN}$, $-\text{OH}$, $-\text{O}(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{NH}_2$, $-\text{NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})_2$, or oxo;

R_3 is 5- or 6-membered heteroaryl optionally substituted with one or more R_{3S} ; and

each R_{3S} independently is halo, $\text{C}_1\text{-C}_6$ alkyl, or $\text{C}_1\text{-C}_6$ haloalkyl.

[0109] In some aspects, the compound is of Formula (I) or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein:



R_1 is , wherein n_{1a} and n_{1b} each independently are 0 or 1;

R_2 is $-(\text{CH}_2)_{n_2}\text{-R}_{2S}$, wherein n_2 is 1 or 2;

R_{2S} is 4- to 8-membered heterocycloalkyl in which at least one heteroatom is O, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with one or more $-\text{OH}$; and

R_3 is 5- or 6-membered heteroaryl optionally substituted with one or more $\text{C}_1\text{-C}_6$ alkyl.

[0110] It is understood that, for a compound of Formula (I), R_1 , R_2 , R_{2S} , R_3 , and R_{3S} can each be, where applicable, selected from the groups described herein, and any group described herein for

any of R_1 , R_2 , R_{2S} , R_3 , and R_{3S} can be combined, where applicable, with any group described herein for one or more of the remainder of R_1 , R_2 , R_{2S} , R_3 , and R_{3S} .

[0111] In some embodiments, n_{1a} is 0.

[0112] In some embodiments, n_{1a} is 1.

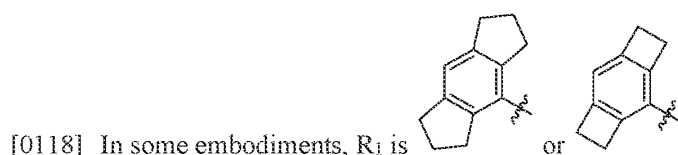
[0113] In some embodiments, n_{1b} is 0.

[0114] In some embodiments, n_{1b} is 1.

[0115] In some embodiments, both of n_{1a} and n_{1b} are 0.

[0116] In some embodiments, one of n_{1a} and n_{1b} is 0, and the other is 1.

[0117] In some embodiments, both of n_{1a} and n_{1b} are 1.



[0121] In some embodiments, R_2 is $-\text{CH}_2-\text{R}_{2S}$.

[0122] In some embodiments, R_2 is $-(\text{CH}_2)_2-\text{R}_{2S}$.

[0123] In some embodiments, R_{2S} is 4- to 8-membered heterocycloalkyl in which at least one heteroatom is O, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with one or more R_{2SS} .

[0124] In some embodiments, R_{2S} is 5- to 6-membered heterocycloalkyl in which at least one heteroatom is O, wherein the 5- to 6-membered heterocycloalkyl is optionally substituted with one or more R_{2SS} .

[0125] In some embodiments, R_{2S} is 4- to 8-membered heterocycloalkyl having one heteroatom, wherein the heteroatom is O, and wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with one or more R_{2SS} .

[0126] In some embodiments, R_{2S} is 5- to 6-membered heterocycloalkyl having one heteroatom, wherein the heteroatom is O, and wherein the 5- to 6-membered heterocycloalkyl is optionally substituted with one or more R_{2SS}.

[0127] In some embodiments, R_{2S} is 5-membered heterocycloalkyl having one heteroatom, wherein the heteroatom is O, and wherein the 5-membered heterocycloalkyl is optionally substituted with one or more R_{2SS}.

[0128] In some embodiments, R_{2S} is 6-membered heterocycloalkyl having one heteroatom, wherein the heteroatom is O, and wherein the 6-membered heterocycloalkyl is optionally substituted with one or more R_{2SS}.

[0129] In some embodiments, each R_{2SS} independently is C₁-C₆ alkyl, halo, -CN, -OH, -NH₂, or oxo.

[0130] In some embodiments, each R_{2SS} independently is -OH or -NH₂.

[0131] In some embodiments, at least one R_{2SS} is -OH.

[0132] In some embodiments, each R_{2SS} is -OH.

[0133] In some embodiments, R_{2S} is 4- to 8-membered heterocycloalkyl in which at least one heteroatom is O, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with one or more C₁-C₆ alkyl, halo, -CN, -OH, -NH₂, or oxo.

[0134] In some embodiments, R_{2S} is 5- to 6-membered heterocycloalkyl in which at least one heteroatom is O, wherein the 5- to 6-membered heterocycloalkyl is optionally substituted with one or more C₁-C₆ alkyl, halo, -CN, -OH, -NH₂, or oxo.

[0135] In some embodiments, R_{2S} is 4- to 8-membered heterocycloalkyl in which at least one heteroatom is O, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with one or more -OH or -NH₂.

[0136] In some embodiments, R_{2S} is 5- to 6-membered heterocycloalkyl in which at least one heteroatom is O, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with one or more -OH or -NH₂.

[0137] In some embodiments, R_{2S} is 4- to 8-membered heterocycloalkyl in which at least one heteroatom is O, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with one or more -OH.

[0138] In some embodiments, R_{2s} is 5- to 6-membered heterocycloalkyl in which at least one heteroatom is O, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with one or more -OH.

[0139] In some embodiments, R_{2s} is 4- to 8-membered heterocycloalkyl having one heteroatom, wherein the heteroatom is O, and wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with one or more -OH.

[0140] In some embodiments, R_{2s} is 5- to 6-membered heterocycloalkyl having one heteroatom, wherein the heteroatom is O, and wherein the 5- to 6-membered heterocycloalkyl is optionally substituted with one or more -OH.

[0141] In some embodiments, R_{2s} is 5-membered heterocycloalkyl having one heteroatom, wherein the heteroatom is O, and wherein the 5-membered heterocycloalkyl is optionally substituted with one or more -OH.

[0142] In some embodiments, R_{2s} is 5-membered heterocycloalkyl having one heteroatom, wherein the heteroatom is O.

[0143] In some embodiments, R_{2s} is 5-membered heterocycloalkyl having one heteroatom, wherein the heteroatom is O, and wherein the 5-membered heterocycloalkyl is substituted with one or more -OH.

[0144] In some embodiments, R_{2s} is 6-membered heterocycloalkyl having one heteroatom, wherein the heteroatom is O, and wherein the 6-membered heterocycloalkyl is optionally substituted with one or more -OH.

[0145] In some embodiments, R_{2s} is 6-membered heterocycloalkyl having one heteroatom, wherein the heteroatom is O.

[0146] In some embodiments, R_{2s} is 6-membered heterocycloalkyl having one heteroatom, wherein the heteroatom is O, and wherein the 6-membered heterocycloalkyl is substituted with one or more -OH.

[0147] In some embodiments, R_{2s} is tetrahydrofuranyl or tetrahydropyranyl, wherein the tetrahydrofuranyl or tetrahydropyranyl is optionally substituted with one or more R_{2ss}.

[0148] In some embodiments, R_{2s} is tetrahydrofuranyl or tetrahydropyranyl, wherein the tetrahydrofuranyl or tetrahydropyranyl is optionally substituted with one or more -OH.

[0149] In some embodiments, R_{2s} is tetrahydrofuranyl or tetrahydropyranyl.

[0150] In some embodiments, R_{2s} is tetrahydrofuranyl or tetrahydropyranyl, wherein the tetrahydrofuranyl or tetrahydropyranyl is substituted with one or more -OH.

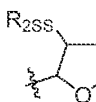
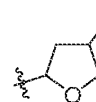
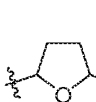
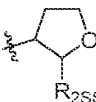
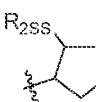
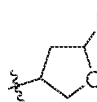
[0151] In some embodiments, R_{2s} is tetrahydrofuranyl optionally substituted with one or more R_{2ss}.

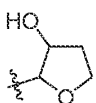
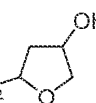
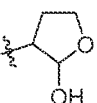
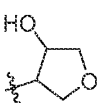
[0152] In some embodiments, R_{2s} is tetrahydrofuranyl optionally substituted with one or more -OH.

[0153] In some embodiments, R_{2s} is tetrahydrofuranyl.

[0154] In some embodiments, R_{2s} is tetrahydrofuranyl substituted with one or more -OH.

[0155] In some embodiments, R_{2s} is  or .

[0156] In some embodiments, R_{2s} is , , , , , or .

[0157] In some embodiments, R_{2s} is , , , or .

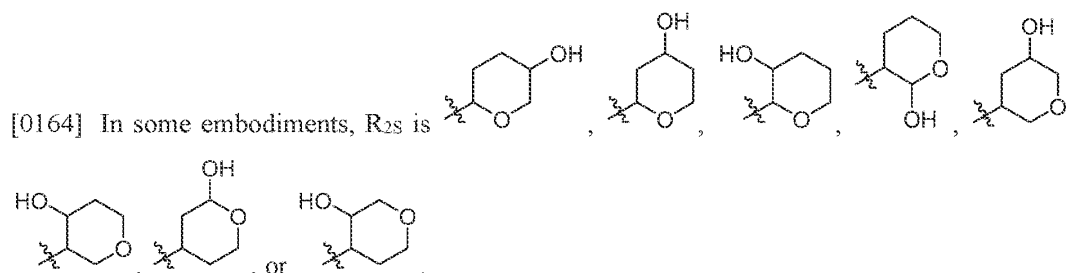
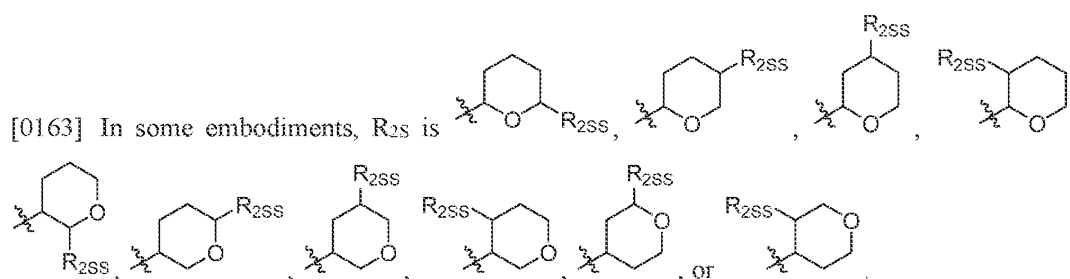
[0158] In some embodiments, R_{2s} is tetrahydropyranyl optionally substituted with one or more R_{2ss}.

[0159] In some embodiments, R_{2s} tetrahydropyranyl optionally substituted with one or more -OH.

[0160] In some embodiments, R_{2s} is tetrahydropyranyl.

[0161] In some embodiments, R_{2s} is tetrahydropyranyl substituted with one or more -OH.

[0162] In some embodiments, R_{2s} is , , or .



[0165] In some embodiments, R₃ is 5- or 6-membered heteroaryl.

[0166] In some embodiments, R₃ is 5- or 6-membered heteroaryl substituted with one or more R_{3S}.

[0167] In some embodiments, R₃ is 5- or 6-membered heteroaryl substituted with one or more C₁-C₆ alkyl (e.g., methyl).

[0168] In some embodiments, R₃ is 5-membered heteroaryl optionally substituted with one or more R_{3S}.

[0169] In some embodiments, R₃ is 5-membered heteroaryl optionally substituted with one or more C₁-C₆ alkyl (e.g., methyl).

[0170] In some embodiments, R₃ is 5-membered heteroaryl.

[0171] In some embodiments, R₃ is 5-membered heteroaryl substituted with one or more R_{3S}.

[0172] In some embodiments, R₃ is 5-membered heteroaryl substituted with one or more C₁-C₆ alkyl (e.g., methyl).

[0173] In some embodiments, R₃ is pyrazolyl optionally substituted with one or more R_{3S}.

[0174] In some embodiments, R₃ is pyrazolyl optionally substituted with one or more C₁-C₆ alkyl (e.g., methyl).

[0175] In some embodiments, R₃ is pyrazolyl.

[0176] In some embodiments, R₃ is pyrazolyl substituted with one or more R_{3S}.

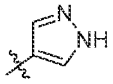
[0177] In some embodiments, R₃ is pyrazolyl substituted with one or more C₁-C₆ alkyl (e.g., methyl).

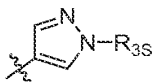
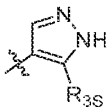
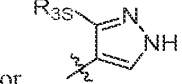
[0178] In some embodiments, each R_{3S} independently is halo.

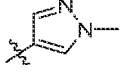
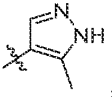
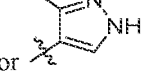
[0179] In some embodiments, each R_{3S} independently is C₁-C₆ alkyl or C₁-C₆ haloalkyl.

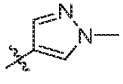
[0180] In some embodiments, each R_{3S} independently is C₁-C₆ alkyl.

[0181] In some embodiments, each R_{3S} is methyl.

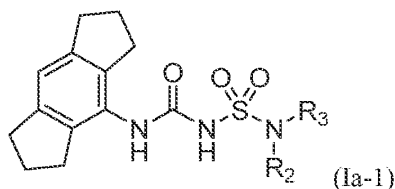
[0182] In some embodiments, R₃ is .

[0183] In some embodiments, R₃ is , , or .

[0184] In some embodiments, R₃ is , , or .

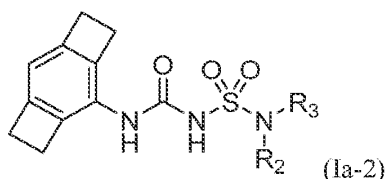
[0185] In some embodiments, R₃ is .

[0186] In some embodiments, the compound is of Formula (Ia-1):



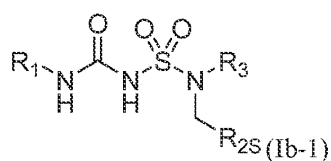
or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein R₂ and R₃ are as described herein.

[0187] In some embodiments, the compound is of Formula (Ia-2):



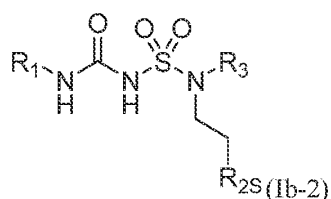
or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein R_{1S}, R₂ and R₃ are as described herein.

[0188] In some embodiments, the compound is of Formula (Ib-1):



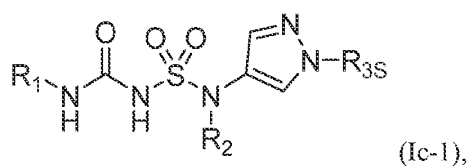
or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein R_1 , R_{2S} , and R_3 are as described herein.

[0189] In some embodiments, the compound is of Formula (Ib-2):



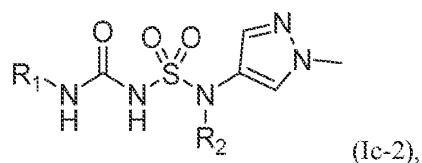
or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein R_1 , R_{2S} , and R_3 are as described herein.

[0190] In some embodiments, the compound is of Formula (Ic-1):



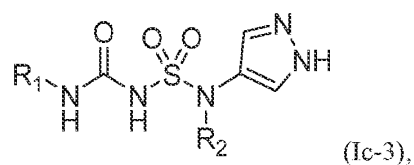
or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein R_1 , R_2 , and R_{3S} are as described herein.

[0191] In some embodiments, the compound is of Formula (Ic-2):



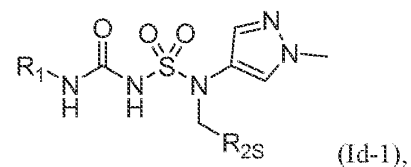
or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein R_1 and R_2 are as described herein.

[0192] In some embodiments, the compound is of Formula (Ic-3):



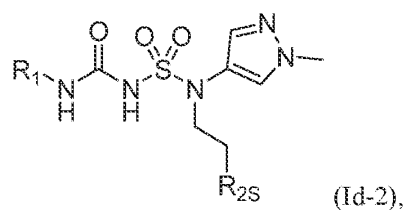
or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein R_1 and R_2 are as described herein.

[0193] In some embodiments, the compound is of Formula (Id-1):



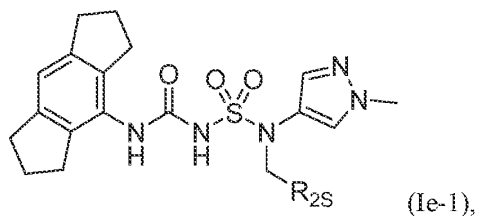
or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein R_1 and R_2 are as described herein.

[0194] In some embodiments, the compound is of Formula (Id-2):



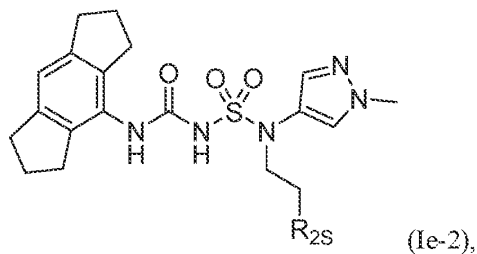
or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein R_1 and R_2 are as described herein.

[0195] In some embodiments, the compound is of Formula (Ie-1):



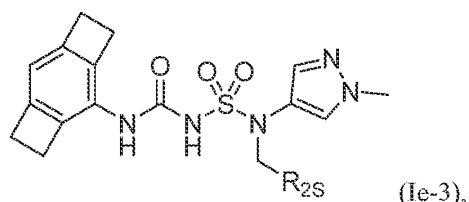
or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein R_2 is as described herein.

[0196] In some embodiments, the compound is of Formula (Ie-2):



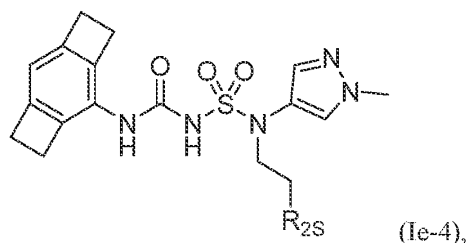
or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein R_{2s} is as described herein.

[0197] In some embodiments, the compound is of Formula (Ie-3):



or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein R_{2s} is as described herein.

[0198] In some embodiments, the compound is of Formula (Ie-4):



or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein R_{2s} is as described herein.

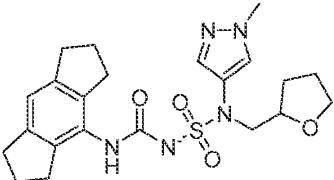
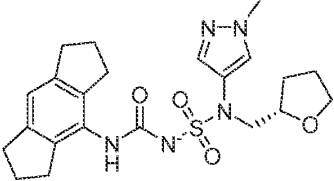
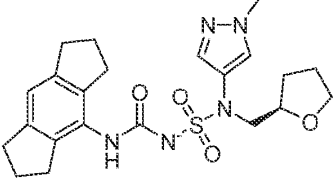
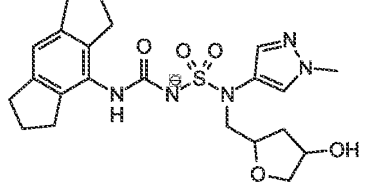
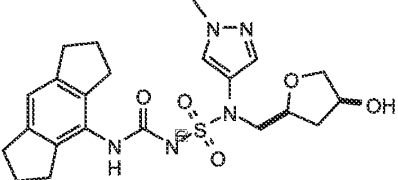
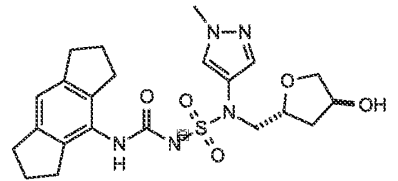
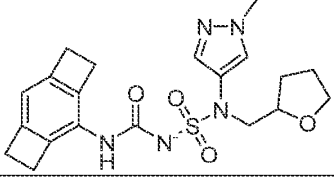
[0199] It is understood that, for a compound of any one of the formulae described herein, R₁, R₂, R_{2s}, R₃, and R_{3s} can each be, where applicable, selected from the groups described herein, and any group described herein for any of R₁, R₂, R_{2s}, R₃, and R_{3s} can be combined, where applicable, with any group described herein for one or more of the remainder of R₁, R₂, R_{2s}, R₃, and R_{3s}.

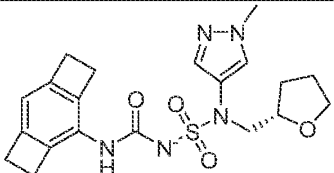
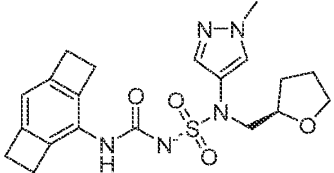
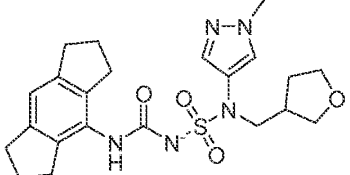
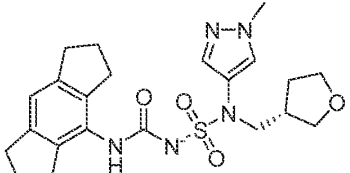
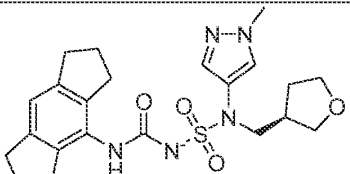
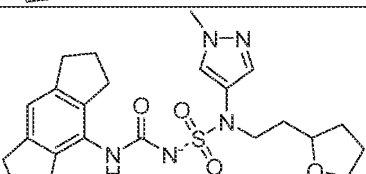
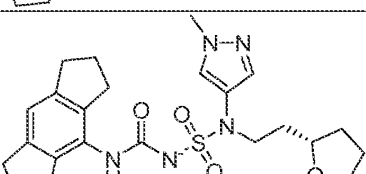
[0200] In some embodiments, the compound is selected from the compounds described in Table 1 and prodrugs and pharmaceutically acceptable salts thereof.

[0201] In some embodiments, the compound is selected from the compounds described in Table 1 and pharmaceutically acceptable salts thereof.

[0202] In some embodiments, the compound is selected from the compounds described in Table 1.

Table 1

Compound No.	Structure
1	
1A	
1B	
2	
2A	
2B	
3	

Compound No.	Structure
3A	
3B	
4	
4A	
4B	
5	
5A	

Compound No.	Structure
5B	
6	
6A	
6B	
7	
7A	
7B	

Compound No.	Structure
8	
8A	
8B	

[0203] In some aspects, the present disclosure provides a compound being an isotopic derivative (e.g., isotopically labeled compound) of any one of the compounds of the Formulae disclosed herein.

[0204] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table 1 and prodrugs and pharmaceutically acceptable salts thereof.

[0205] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table 1 and pharmaceutically acceptable salts thereof.

[0206] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table 1.

[0207] It is understood that the isotopic derivative can be prepared using any of a variety of art-recognised techniques. For example, the isotopic derivative can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples described herein, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

[0208] In some embodiments, the isotopic derivative is a deuterium labeled compound.

[0209] In some embodiments, the isotopic derivative is a deuterium labeled compound of any one of the compounds of the Formulae disclosed herein.

[0210] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Table 1 and prodrugs and pharmaceutically acceptable salts thereof.

[0211] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Table 1 and pharmaceutically acceptable salts thereof.

[0212] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Table 1.

[0213] It is understood that the deuterium labeled compound comprises a deuterium atom having an abundance of deuterium that is substantially greater than the natural abundance of deuterium, which is 0.015%.

[0214] In some embodiments, the deuterium labeled compound has a deuterium enrichment factor for each deuterium atom of at least 3500 (52.5% deuterium incorporation at each deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation). As used herein, the term “deuterium enrichment factor” means the ratio between the deuterium abundance and the natural abundance of a deuterium.

[0215] It is understood that the deuterium labeled compound can be prepared using any of a variety of art-recognised techniques. For example, the deuterium labeled compound can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples described herein, by substituting a deuterium labeled reagent for a non-deuterium labeled reagent.

[0216] A compound of the invention or a pharmaceutically acceptable salt or solvate thereof that contains the aforementioned deuterium atom(s) is within the scope of the invention. Further, substitution with deuterium (*i.e.*, ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability, *e.g.*, increased *in vivo* half-life or reduced dosage requirements.

[0217] For the avoidance of doubt it is to be understood that, where in this specification a group is qualified by “described herein”, the said group encompasses the first occurring and broadest definition as well as each and all of the particular definitions for that group.

[0218] A suitable pharmaceutically acceptable salt of a compound of the disclosure is, for example, an acid-addition salt of a compound of the disclosure which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, formic, citric methane sulphonate or maleic acid. In addition, a suitable pharmaceutically acceptable salt of a compound

of the disclosure which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a pharmaceutically acceptable cation, for example a salt with methylamine, dimethylamine, diethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

[0219] It will be understood that the compounds of any one of the Formulae disclosed herein and any pharmaceutically acceptable salts thereof, comprise stereoisomers, mixtures of stereoisomers, polymorphs of all isomeric forms of said compounds.

[0220] As used herein, the term “isomerism” means compounds that have identical molecular formulae but differ in the sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers.” Stereoisomers that are not mirror images of one another are termed “diastereoisomers,” and stereoisomers that are non-superimposable mirror images of each other are termed “enantiomers” or sometimes optical isomers. A mixture containing equal amounts of individual enantiomeric forms of opposite chirality is termed a “racemic mixture.”

[0221] As used herein, the term “chiral centre” refers to a carbon atom bonded to four nonidentical substituents.

[0222] As used herein, the term “chiral isomer” means a compound with at least one chiral centre. Compounds with more than one chiral centre may exist either as an individual diastereomer or as a mixture of diastereomers, termed “diastereomeric mixture.” When one chiral centre is present, a stereoisomer may be characterised by the absolute configuration (R or S) of that chiral centre. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral centre. The substituents attached to the chiral centre under consideration are ranked in accordance with the *Sequence Rule* of Cahn, Ingold and Prelog. (Cahn *et al.*, *Angew. Chem. Inter. Edit.* 1966, 5, 385; errata 511; Cahn *et al.*, *Angew. Chem.* 1966, 78, 413; Cahn and Ingold, *J. Chem. Soc.* 1951 (London), 612; Cahn *et al.*, *Experientia* 1956, 12, 81; Cahn, *J. Chem. Educ.* 1964, 41, 116).

[0223] As used herein, the term “geometric isomer” means the diastereomers that owe their existence to hindered rotation about double bonds or a cycloalkyl linker (e.g., 1,3-cyclobutyl). These configurations are differentiated in their names by the prefixes cis and trans, or Z and E, which indicate that the groups are on the same or opposite side of the double bond in the molecule according to the Cahn-Ingold-Prelog rules.

[0224] It is to be understood that the compounds of the present disclosure may be depicted as different chiral isomers or geometric isomers. It is also to be understood that when compounds have chiral isomeric or geometric isomeric forms, all isomeric forms are intended to be included in the scope of the present disclosure, and the naming of the compounds does not exclude any isomeric forms, it being understood that not all isomers may have the same level of activity.

[0225] It is to be understood that the structures and other compounds discussed in this disclosure include all atropic isomers thereof. It is also to be understood that not all atropic isomers may have the same level of activity.

[0226] As used herein, the term “atropic isomers” are a type of stereoisomer in which the atoms of two isomers are arranged differently in space. Atropic isomers owe their existence to a restricted rotation caused by hindrance of rotation of large groups about a central bond. Such atropic isomers typically exist as a mixture, however as a result of recent advances in chromatography techniques, it has been possible to separate mixtures of two atropic isomers in select cases.

[0227] As used herein, the term “tautomer” is one of two or more structural isomers that exist in equilibrium and is readily converted from one isomeric form to another. This conversion results in the formal migration of a hydrogen atom accompanied by a switch of adjacent conjugated double bonds. Tautomers exist as a mixture of a tautomeric set in solution. In solutions where tautomerisation is possible, a chemical equilibrium of the tautomers will be reached. The exact ratio of the tautomers depends on several factors, including temperature, solvent and pH. The concept of tautomers that are interconvertible by tautomerisations is called tautomerism. Of the various types of tautomerism that are possible, two are commonly observed. In keto-enol tautomerism a simultaneous shift of electrons and a hydrogen atom occurs. Ring-chain tautomerism arises as a result of the aldehyde group (-CHO) in a sugar chain molecule reacting with one of the hydroxy groups (-OH) in the same molecule to give it a cyclic (ring-shaped) form as exhibited by glucose.

[0228] It is to be understood that the compounds of the present disclosure may be depicted as different tautomers. It should also be understood that when compounds have tautomeric forms, all tautomeric forms are intended to be included in the scope of the present disclosure, and the naming of the compounds does not exclude any tautomer form. It will be understood that certain tautomers may have a higher level of activity than others.

[0229] Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed “isomers”. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers”. Stereoisomers that are not mirror images of one another are termed “diastereomers” and those that are non-superimposable mirror images of each other are termed “enantiomers”. When a compound has an asymmetric centre, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterised by the absolute configuration of its asymmetric centre and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarised light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a “racemic mixture”.

[0230] The compounds of this disclosure may possess one or more asymmetric centres; such compounds can therefore be produced as individual (R)- or (S)-stereoisomers or as mixtures thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of “Advanced Organic Chemistry”, 4th edition J. March, John Wiley and Sons, New York, 2001), for example by synthesis from optically active starting materials or by resolution of a racemic form. Some of the compounds of the disclosure may have geometric isomeric centres (E- and Z- isomers). It is to be understood that the present disclosure encompasses all optical, diastereoisomers and geometric isomers and mixtures thereof that possess inflammasome inhibitory activity.

[0231] The present disclosure also encompasses compounds of the disclosure as defined herein which comprise one or more isotopic substitutions.

[0232] It is to be understood that the compounds of any Formula described herein include the compounds themselves, as well as their salts, and their solvates, if applicable. A salt, for example, can be formed between an anion and a positively charged group (e.g., amino) on a substituted compound disclosed herein. Suitable anions include chloride, bromide, iodide, sulphate, bisulphate, sulphamate, nitrate, phosphate, citrate, methanesulphonate, trifluoroacetate, glutamate,

glucuronate, glutarate, malate, maleate, succinate, fumarate, tartrate, tosylate, salicylate, lactate, naphthalenesulphonate, and acetate (e.g., trifluoroacetate).

[0233] As used herein, the term “pharmaceutically acceptable anion” refers to an anion suitable for forming a pharmaceutically acceptable salt. Likewise, a salt can also be formed between a cation and a negatively charged group (e.g., carboxylate) on a substituted compound disclosed herein. Suitable cations include sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion or diethylamine ion. The substituted compounds disclosed herein also include those salts containing quaternary nitrogen atoms.

[0234] It is to be understood that the compounds of the present disclosure, for example, the salts of the compounds, can exist in either hydrated or unhydrated (the anhydrous) form or as solvates with other solvent molecules. Nonlimiting examples of hydrates include monohydrates, dihydrates, etc. Nonlimiting examples of solvates include ethanol solvates, acetone solvates, etc.

[0235] As used herein, the term “solvate” means solvent addition forms that contain either stoichiometric or non-stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water the solvate formed is a hydrate; and if the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one molecule of the substance in which the water retains its molecular state as H₂O.

[0236] As used herein, the term “analog” refers to a chemical compound that is structurally similar to another but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group, or the replacement of one functional group by another functional group). Thus, an analog is a compound that is similar or comparable in function and appearance, but not in structure or origin to the reference compound.

[0237] As used herein, the term “derivative” refers to compounds that have a common core structure and are substituted with various groups as described herein.

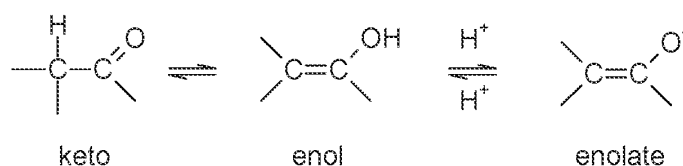
[0238] As used herein, the term “bioisostere” refers to a compound resulting from the exchange of an atom or of a group of atoms with another, broadly similar, atom or group of atoms. The objective of a bioisosteric replacement is to create a new compound with similar biological properties to the parent compound. The bioisosteric replacement may be physicochemically or topologically based. Examples of carboxylic acid bioisosteres include, but are not limited to, acyl

sulphonamides, tetrazoles, sulphonates and phosphonates. See, *e.g.*, Patani and LaVoie, *Chem. Rev.* 96, 3147-3176, 1996.

[0239] It is also to be understood that certain compounds of any one of the Formulae disclosed herein may exist in solvated as well as unsolvated forms such as, for example, hydrated forms. A suitable pharmaceutically acceptable solvate is, for example, a hydrate such as hemi-hydrate, a mono-hydrate, a di-hydrate or a tri-hydrate. It is to be understood that the disclosure encompasses all such solvated forms that possess inflammasome inhibitory activity.

[0240] It is also to be understood that certain compounds of any one of the Formulae disclosed herein may exhibit polymorphism, and that the disclosure encompasses all such forms, or mixtures thereof, which possess inflammasome inhibitory activity. It is generally known that crystalline materials may be analysed using conventional techniques such as X-Ray Powder Diffraction analysis, Differential Scanning Calorimetry, Thermal Gravimetric Analysis, Diffuse Reflectance Infrared Fourier Transform (DRIFT) spectroscopy, Near Infrared (NIR) spectroscopy, solution and/or solid state nuclear magnetic resonance spectroscopy. The water content of such crystalline materials may be determined by Karl Fischer analysis.

[0241] Compounds of any one of the Formulae disclosed herein may exist in a number of different tautomeric forms and references to compounds of Formula (I) include all such forms. For the avoidance of doubt, where a compound can exist in one of several tautomeric forms, and only one is specifically described or shown, all others are nevertheless embraced by Formula (I). Examples of tautomeric forms include keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, and nitro/aci-nitro.



[0242] Compounds of any one of the Formulae disclosed herein containing an amine function may also form N-oxides. A reference herein to a compound of Formula (I) that contains an amine function also includes the N-oxide. Where a compound contains several amine functions, one or more than one nitrogen atom may be oxidised to form an N-oxide. Particular examples of N-oxides are the N-oxides of a tertiary amine or a nitrogen atom of a nitrogen-containing heterocycle. N-

oxides can be formed by treatment of the corresponding amine with an oxidising agent such as hydrogen peroxide or a peracid (e.g. a peroxycarboxylic acid), see for example Advanced Organic Chemistry, by Jerry March, 4th Edition, Wiley Interscience, pages. More particularly, N-oxides can be made by the procedure of L. W. Deady (Syn. Comm. 1977, 7, 509-514) in which the amine compound is reacted with meta-chloroperoxybenzoic acid (mCPBA), for example, in an inert solvent such as dichloromethane.

[0243] The compounds of any one of the Formulae disclosed herein may be administered in the form of a prodrug which is broken down in the human or animal body to release a compound of the disclosure. A prodrug may be used to alter the physical properties and/or the pharmacokinetic properties of a compound of the disclosure. A prodrug can be formed when the compound of the disclosure contains a suitable group or substituent to which a property-modifying group can be attached. Examples of prodrugs include derivatives containing *in vivo* cleavable alkyl or acyl substituents at the sulphonylurea group in a compound of the any one of the Formulae disclosed herein.

[0244] Accordingly, the present disclosure includes those compounds of any one of the Formulae disclosed herein as defined hereinbefore when made available by organic synthesis and when made available within the human or animal body by way of cleavage of a prodrug thereof. Accordingly, the present disclosure includes those compounds of any one of the Formulae disclosed herein that are produced by organic synthetic means and also such compounds that are produced in the human or animal body by way of metabolism of a precursor compound, that is a compound of any one of the Formulae disclosed herein may be a synthetically-produced compound or a metabolically-produced compound.

[0245] A suitable pharmaceutically acceptable prodrug of a compound of any one of the Formulae disclosed herein is one that is based on reasonable medical judgment as being suitable for administration to the human or animal body without undesirable pharmacological activities and without undue toxicity. Various forms of prodrug have been described, for example in the following documents: a) Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985); b) Design of Pro-drugs, edited by H. Bundgaard, (Elsevier, 1985); c) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Pro-drugs", by H. Bundgaard p. 113-191 (1991); d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992); e) H. Bundgaard, et al., Journal of

Pharmaceutical Sciences, 77, 285 (1988); f) N. Kakeya, et al., Chem. Pharm. Bull., 32, 692 (1984); g) T. Higuchi and V. Stella, "Pro-Drugs as Novel Delivery Systems", A.C.S. Symposium Series, Volume 14; and h) E. Roche (editor), "Bioreversible Carriers in Drug Design", Pergamon Press, 1987.

[0246] A suitable pharmaceutically acceptable prodrug of a compound of any one of the Formulae disclosed herein that possesses a hydroxy group is, for example, an *in vivo* cleavable ester or ether thereof. An *in vivo* cleavable ester or ether of a compound of any one of the Formulae disclosed herein containing a hydroxy group is, for example, a pharmaceutically acceptable ester or ether which is cleaved in the human or animal body to produce the parent hydroxy compound. Suitable pharmaceutically acceptable ester forming groups for a hydroxy group include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters). Further suitable pharmaceutically acceptable ester forming groups for a hydroxy group include C₁-C₁₀ alkanoyl groups such as acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups, C₁-C₁₀ alkoxycarbonyl groups such as ethoxycarbonyl, N,N-(C₁-C₆ alkyl)₂carbamoyl, 2-dialkylaminoacetyl and 2-carboxyacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, N-alkylaminomethyl, N,N-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-(C₁-C₄ alkyl)piperazin-1-ylmethyl. Suitable pharmaceutically acceptable ether forming groups for a hydroxy group include α -acyloxyalkyl groups such as acetoxymethyl and pivaloyloxymethyl groups.

[0247] A suitable pharmaceutically acceptable prodrug of a compound of any one of the Formulae disclosed herein that possesses a carboxy group is, for example, an *in vivo* cleavable amide thereof, for example an amide formed with an amine such as ammonia, a C₁₋₄alkylamine such as methylamine, a (C₁-C₄ alkyl)₂amine such as dimethylamine, N-ethyl-N-methylamine or diethylamine, a C₁-C₄ alkoxy-C₂-C₄ alkylamine such as 2-methoxyethylamine, a phenyl-C₁-C₄ alkylamine such as benzylamine and amino acids such as glycine or an ester thereof.

[0248] A suitable pharmaceutically acceptable prodrug of a compound of any one of the Formulae disclosed herein that possesses an amino group is, for example, an *in vivo* cleavable amide derivative thereof. Suitable pharmaceutically acceptable amides from an amino group include, for example an amide formed with C₁-C₁₀ alkanoyl groups such as an acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, N-alkylaminomethyl, N,N-

dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-(C₁-C₄ alkyl)piperazin-1-ylmethyl.

[0249] The *in vivo* effects of a compound of any one of the Formulae disclosed herein may be exerted in part by one or more metabolites that are formed within the human or animal body after administration of a compound of any one of the Formulae disclosed herein. As stated hereinbefore, the *in vivo* effects of a compound of any one of the Formulae disclosed herein may also be exerted by way of metabolism of a precursor compound (a prodrug).

[0250] Suitably, the present disclosure excludes any individual compounds not possessing the biological activity defined herein.

Methods of Synthesis

[0251] In some aspects, the present disclosure provides a method of preparing a compound of the present disclosure.

[0252] In some aspects, the present disclosure provides a method of a compound, comprising one or more steps as described herein.

[0253] In some aspects, the present disclosure provides a compound obtainable by, or obtained by, or directly obtained by a method for preparing a compound as described herein.

[0254] In some aspects, the present disclosure provides an intermediate as described herein, being suitable for use in a method for preparing a compound as described herein.

[0255] The compounds of the present disclosure can be prepared by any suitable technique known in the art. Particular processes for the preparation of these compounds are described further in the accompanying examples.

[0256] In the description of the synthetic methods described herein and in any referenced synthetic methods that are used to prepare the starting materials, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, can be selected by a person skilled in the art.

[0257] It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reaction conditions utilised.

[0258] It will be appreciated that during the synthesis of the compounds of the disclosure in the processes defined herein, or during the synthesis of certain starting materials, it may be desirable to protect certain substituent groups to prevent their undesired reaction. The skilled chemist will appreciate when such protection is required, and how such protecting groups may be put in place, and later removed. For examples of protecting groups see one of the many general texts on the subject, for example, 'Protective Groups in Organic Synthesis' by Theodora Green (publisher: John Wiley & Sons). Protecting groups may be removed by any convenient method described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with the minimum disturbance of groups elsewhere in the molecule. Thus, if reactants include, for example, groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

[0259] By way of example, a suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or t-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed by, for example, hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a tert-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium on carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

[0260] A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an

alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium, sodium hydroxide or ammonia. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium on carbon.

[0261] A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a tert-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium on carbon.

[0262] Once a compound of Formula (I) has been synthesised by any one of the processes defined herein, the processes may then further comprise the additional steps of: (i) removing any protecting groups present; (ii) converting the compound Formula (I) into another compound of Formula (I); (iii) forming a pharmaceutically acceptable salt, hydrate or solvate thereof; and/or (iv) forming a prodrug thereof.

[0263] The resultant compounds of Formula (I) can be isolated and purified using techniques well known in the art.

[0264] Conveniently, the reaction of the compounds is carried out in the presence of a suitable solvent, which is preferably inert under the respective reaction conditions. Examples of suitable solvents comprise but are not limited to hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichlorethylene, 1,2-dichloroethane, tetrachloromethane, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF), 2-methyltetrahydrofuran, cyclopentylmethyl ether (CPME), methyl tert-butyl ether (MTBE) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether (diglyme); ketones, such as acetone, methylisobutylketone (MIBK) or butanone; amides, such as acetamide, dimethylacetamide, dimethylformamide (DMF) or N-methylpyrrolidinone (NMP); nitriles, such as acetonitrile; sulphoxides, such as dimethyl sulphoxide (DMSO); nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate or methyl acetate, or mixtures of the said solvents or mixtures with water.

[0265] The reaction temperature is suitably between about -100 °C and 300 °C, depending on the reaction step and the conditions used.

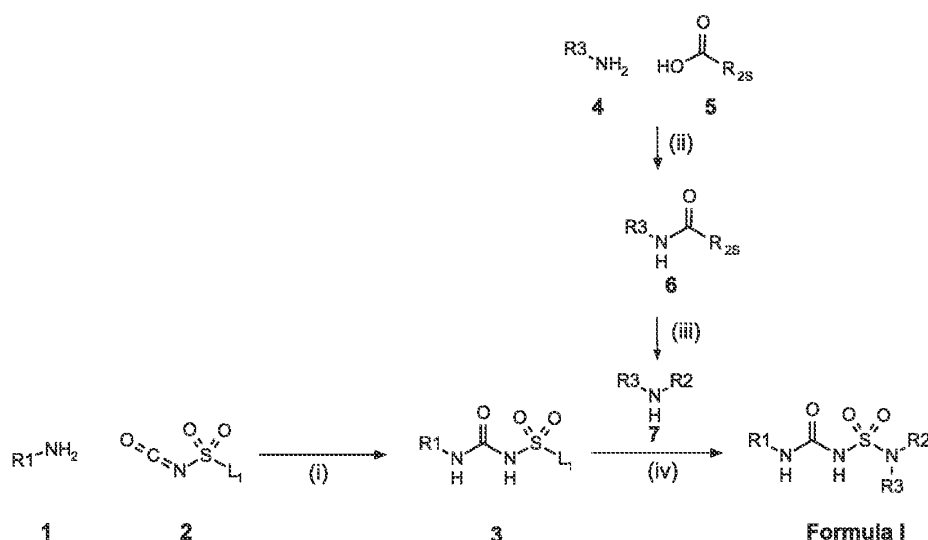
[0266] Reaction times are generally in the range between a fraction of a minute and several days, depending on the reactivity of the respective compounds and the respective reaction conditions. Suitable reaction times are readily determinable by methods known in the art, for example reaction monitoring. Based on the reaction temperatures given above, suitable reaction times generally lie in the range between 10 minutes and 48 hours.

[0267] Moreover, by utilising the procedures described herein, in conjunction with ordinary skills in the art, additional compounds of the present disclosure can be readily prepared. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.

[0268] As will be understood by the person skilled in the art of organic synthesis, compounds of the present disclosure are readily accessible by various synthetic routes, some of which are exemplified in the accompanying examples. The skilled person will easily recognise which kind of reagents and reactions conditions are to be used and how they are to be applied and adapted in any particular instance – wherever necessary or useful – in order to obtain the compounds of the present disclosure. Furthermore, some of the compounds of the present disclosure can readily be synthesised by reacting other compounds of the present disclosure under suitable conditions, for instance, by converting one particular functional group being present in a compound of the present disclosure, or a suitable precursor molecule thereof, into another one by applying standard synthetic methods, like reduction, oxidation, addition or substitution reactions; those methods are well known to the skilled person. Likewise, the skilled person will apply – whenever necessary or useful – synthetic protecting (or protective) groups; suitable protecting groups as well as methods for introducing and removing them are well-known to the person skilled in the art of chemical synthesis and are described, in more detail, in, e.g., P.G.M. Wuts, T.W. Greene, “Greene’s Protective Groups in Organic Synthesis”, 4th edition (2006) (John Wiley & Sons).

[0269] General routes for the preparation of a compound of the application are described in Schemes 1-2 herein.

Scheme 1



[0270] In Scheme 1, L₁ is a suitable leaving group (e.g., Cl or another halide).

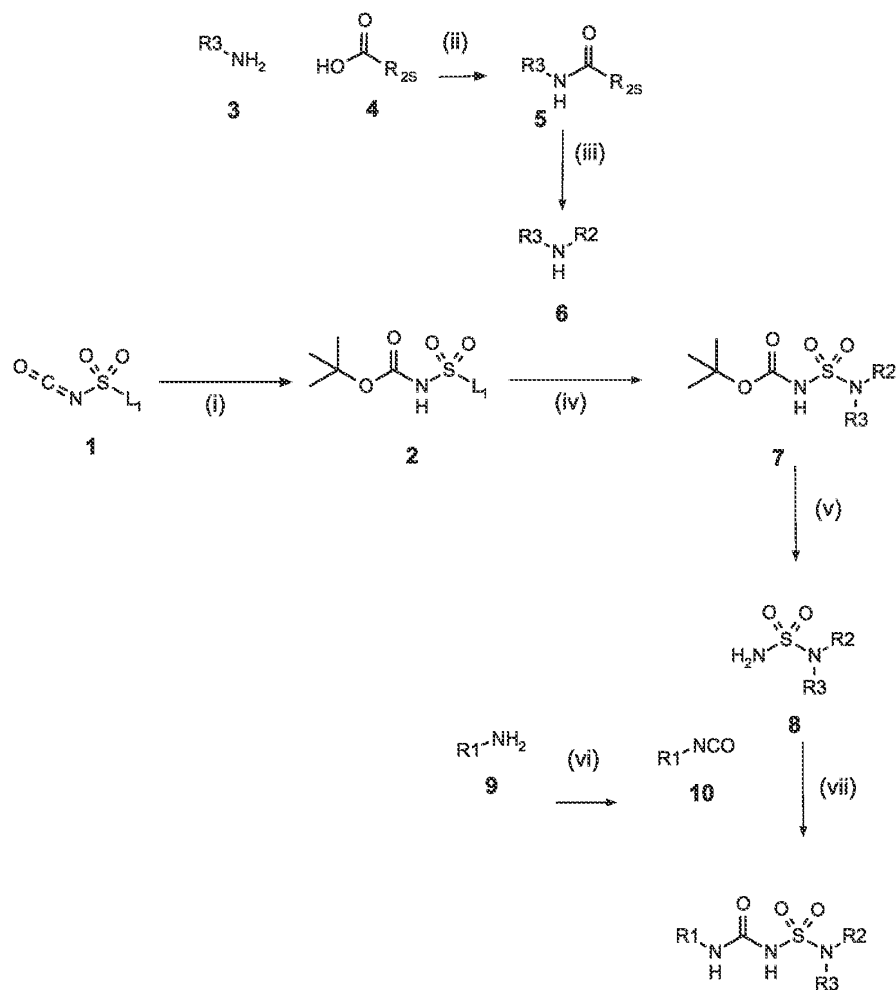
[0271] Reaction (i) may be performed by reacting amine **1** with isocyanate **2** in a suitable solvent (e.g., diisopropyl ether or dichloromethane) and, optionally, at a cooled temperature (e.g., 0° C or -15° C), yielding Intermediate **3**. In some embodiments, Intermediate **3** may be used directly as a solution and not isolated.

[0272] Reaction (ii) may be performed by reacting amine **4** with acid **5** in a suitable solvent (e.g., DMF), in the presence of a coupling agent (e.g., HATU or EDCI), yielding Intermediate **6**.

[0273] Reaction (iii) may be performed by reacting amide **6** with a suitable reducing agent (e.g., LiAlH₄) in a suitable solvent (e.g., THF) and, optionally with heating (e.g., to 70° C). Intermediate **7** may be isolated by purification (e.g., by flash column chromatography or by preparative HPLC). In some embodiments, Intermediate **7** is isolated as a free amine or as a salt (e.g., trifluoroacetate salt).

[0274] Reaction (iv) may be performed by reacting intermediate **3** with Intermediate **7** in a suitable solvent (e.g., tetrahydrofuran), in the presence of a base (e.g., sodium hydride or sodium hydroxide) and, optionally, in the presence of a catalyst (e.g., 4-(dimethylamino)-pyridine), yielding a compound of Formula (I). The compound of Formula (I) may be isolated by purification (e.g., by flash column chromatography or by preparative HPLC). In some embodiments, the compounds of Formula (I) is isolated as a neutral compound or as a salt (e.g., sodium salt).

Scheme 2



Formula I

[0275] In Scheme 2, L_1 is a suitable leaving group (e.g., Cl or another halide).

[0276] Reaction (i) may be performed by reacting isocyanate **1** with tert-butanol in a suitable solvent (e.g., tetrahydrofuran) and, optionally, at a cooled temperature (e.g., $0^\circ C$), yielding Intermediate **2**. In some embodiments, Intermediate **2** is then used directly as a solution and not directly isolated.

[0277] Reaction (ii) may be performed by reacting amine **3** with acid **4** in a suitable solvent (e.g., DMF), in the presence of a coupling agent (e.g., HATU or EDCI), yielding Intermediate **5**.

[0278] Reaction (iii) may be performed by reacting amide **5** with a suitable reducing agent (e.g., LiAlH_4) in a suitable solvent (e.g., THF) and, optionally with heating (e.g., to 70°C). Intermediate **6** may be isolated by purification (e.g., by flash column chromatography or by preparative HPLC). In some embodiments, Intermediate **7** is isolated as a free amine or as a salt (e.g., trifluoroacetate salt).

[0279] Reaction (iv) may be performed by reacting Intermediate **6** with intermediate **2** in a suitable solvent (e.g., tetrahydrofuran) and in the presence of a base (e.g., diisopropylethyl-amine), yielding Intermediate **7**. Intermediate **7** may be isolated by purification (e.g., by flash column chromatography or by preparative HPLC).

[0280] Reaction (v) may be performed by reacting intermediate **7** with a suitable acid (e.g., hydrochloric acid or trifluoroacetic acid), in a suitable solvent (e.g., 1,4-dioxane or dichloromethane) and, optionally, at a cooled temperature (e.g., 0°C), yielding Intermediate **8**. Intermediate **8** may be isolated by purification (e.g., by flash column chromatography or by preparative HPLC). In some embodiments, Intermediate **8** is isolated as a free amine or as a salt (e.g., trifluoroacetate salt).

[0281] Reaction (vi) may be performed by reacting primary amine **9** with a suitable reagent (e.g., triphosgene), in the presence of a suitable base (e.g., diisopropylethylamine or triethylamine) and in the presence of a suitable solvent (e.g., 1,4-dioxane) and, optionally, at an elevated temperature (e.g., 40°C), yielding Intermediate **10**.

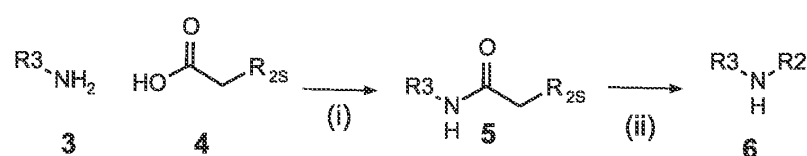
[0282] Reaction (vii) may be performed by reacting Intermediate **8** with Intermediate **10** in a suitable solvent (e.g., tetrahydrofuran), in the presence of a base (e.g., sodium hydride or sodium hydroxide) and, optionally, in the presence of a catalyst (e.g., 4-(dimethylamino)-pyridine), yielding a compound of Formula (I). In some embodiments, reaction (vii) may be performed at a cooled temperature (e.g., example 0°C). The compound of Formula (I) may be isolated by purification (e.g., by flash column chromatography or by preparative HPLC). In some embodiments, the compound of Formula (I) is isolated as a neutral compound or as a salt (e.g., sodium salt).

[0283] It should be understood that in the description and formulae shown above, the various groups are as defined herein, except where otherwise indicated. Furthermore, for synthetic purposes, the compounds in the Schemes are mere representatives with elected substituents to illustrate the general synthetic methodology of a compound disclosed herein.

[0284] It is understood that a neutral compound of Formula (I) may be converted to a salt (e.g., sodium salt) using routine techniques in the art (e.g., pH adjustment and, optionally, extraction (e.g., into an organic phase)). Further, a salt (e.g., sodium salt) of a compound of Formula (I) may be converted to a neutral compound using routine techniques in the art (e.g., pH adjustment and, optionally, extraction (e.g., into an aqueous phase)).

[0285] Where the compounds include a CH_2CH_2 spacer (i.e., R_2 is $-(\text{CH}_2)_{n2}-\text{R}_{2s}$, wherein n_2 is 2), the intermediate **6** can be prepared as in Scheme 3 using the reactions described above.

Scheme 3



Biological Assays

[0286] Compounds designed, selected and/or optimised by methods described above, once produced, can be characterised using a variety of assays known to those skilled in the art to determine whether the compounds have biological activity. For example, the molecules can be characterised by conventional assays, including but not limited to those assays described below, to determine whether they have a predicted activity, binding activity and/or binding specificity.

[0287] Furthermore, high-throughput screening can be used to speed up analysis using such assays. As a result, it can be possible to rapidly screen the molecules described herein for activity, using techniques known in the art. General methodologies for performing high-throughput screening are described, for example, in Devlin (1998) *High Throughput Screening*, Marcel Dekker; and U.S. Patent No. 5,763,263. High-throughput assays can use one or more different assay techniques including, but not limited to, those described below.

[0288] Various *in vitro* or *in vivo* biological assays may be suitable for detecting the effect of the compounds of the present disclosure. These *in vitro* or *in vivo* biological assays can include, but are not limited to, enzymatic activity assays, electrophoretic mobility shift assays, reporter gene assays, *in vitro* cell viability assays, and the assays described herein.

[0289] In some embodiments, the biological assay is a biological assay testing inhibitory activity against IL-1 β release upon NLRP3 activation in peripheral blood mononuclear cells (PBMC).

[0290] In some embodiments, the biological assay is a PBMC IC₅₀ Determination Assay. In some embodiments, the biological assay is a PBMC IC₅₀ Determination Assay.

Pharmaceutical Compositions

[0291] In some aspects, the present disclosure provides a pharmaceutical composition comprising a compound of the present disclosure as an active ingredient.

[0292] In some embodiments, the present disclosure provides a pharmaceutical composition comprising a compound described herein and one or more pharmaceutically acceptable carriers or excipients. In some embodiments, the present disclosure provides a pharmaceutical composition comprising at least one compound selected from Table 1.

[0293] As used herein, the term “composition” is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

[0294] The compounds of present disclosure can be formulated for oral administration in forms such as tablets, capsules (each of which includes sustained release or timed-release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups and emulsions. The compounds of present disclosure can also be formulated for intravenous (bolus or infusion), intraperitoneal, topical, subcutaneous, intramuscular or transdermal (e.g., patch) administration, all using forms well known to those of ordinary skill in the pharmaceutical arts.

[0295] The formulation of the present disclosure may be in the form of an aqueous solution comprising an aqueous vehicle. The aqueous vehicle component may comprise water and at least one pharmaceutically acceptable excipient. Suitable acceptable excipients include those selected from the group consisting of a solubility enhancing agent, chelating agent, preservative, tonicity agent, viscosity/suspending agent, buffer, and pH modifying agent, and a mixture thereof.

[0296] Any suitable solubility enhancing agent can be used. Examples of a solubility enhancing agent include cyclodextrin, such as those selected from the group consisting of hydroxypropyl- β -cyclodextrin, methyl- β -cyclodextrin, randomly methylated- β -cyclodextrin, ethylated- β -cyclodextrin, triacetyl- β -cyclodextrin, peracetylated- β -cyclodextrin, carboxymethyl- β -cyclodextrin, hydroxyethyl- β -cyclodextrin, 2-hydroxy-3-(trimethylammonio)propyl- β -cyclodextrin, glucosyl- β -cyclodextrin, sulphated β -cyclodextrin (S- β -CD), maltosyl- β -cyclodextrin, β -cyclodextrin sulphobutyl ether, branched- β -cyclodextrin, hydroxypropyl- γ -

cyclodextrin, randomly methylated- γ -cyclodextrin, and trimethyl- γ -cyclodextrin, and mixtures thereof.

[0297] Any suitable chelating agent can be used. Examples of a suitable chelating agent include those selected from the group consisting of ethylenediaminetetraacetic acid and metal salts thereof, disodium edetate, trisodium edetate, and tetrasodium edetate, and mixtures thereof.

[0298] Any suitable preservative can be used. Examples of a preservative include those selected from the group consisting of quaternary ammonium salts such as benzalkonium halides (preferably benzalkonium chloride), chlorhexidine gluconate, benzethonium chloride, cetyl pyridinium chloride, benzyl bromide, phenylmercury nitrate, phenylmercury acetate, phenylmercury neodecanoate, merthiolate, methylparaben, propylparaben, sorbic acid, potassium sorbate, sodium benzoate, sodium propionate, ethyl p-hydroxybenzoate, propylaminopropyl biguanide, and butyl-p-hydroxybenzoate, and sorbic acid, and mixtures thereof.

[0299] The aqueous vehicle may also include a tonicity agent to adjust the tonicity (osmotic pressure). The tonicity agent can be selected from the group consisting of a glycol (such as propylene glycol, diethylene glycol, triethylene glycol), glycerol, dextrose, glycerin, mannitol, potassium chloride, and sodium chloride, and a mixture thereof.

[0300] The aqueous vehicle may also contain a viscosity/suspending agent. Suitable viscosity/suspending agents include those selected from the group consisting of cellulose derivatives, such as methyl cellulose, ethyl cellulose, hydroxyethylcellulose, polyethylene glycols (such as polyethylene glycol 300, polyethylene glycol 400), carboxymethyl cellulose, hydroxypropylmethyl cellulose, and cross-linked acrylic acid polymers (carbomers), such as polymers of acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol (Carbopols - such as Carbopol 934, Carbopol 934P, Carbopol 971, Carbopol 974 and Carbopol 974P), and a mixture thereof.

[0301] In order to adjust the formulation to an acceptable pH (typically a pH range of about 5.0 to about 9.0, more preferably about 5.5 to about 8.5, particularly about 6.0 to about 8.5, about 7.0 to about 8.5, about 7.2 to about 7.7, about 7.1 to about 7.9, or about 7.5 to about 8.0), the formulation may contain a pH modifying agent. The pH modifying agent is typically a mineral acid or metal hydroxide base, selected from the group of potassium hydroxide, sodium hydroxide, and hydrochloric acid, and mixtures thereof, and preferably sodium hydroxide and/or hydrochloric acid. These acidic and/or basic pH modifying agents are added to adjust the formulation to the

target acceptable pH range. Hence it may not be necessary to use both acid and base - depending on the formulation, the addition of one of the acid or base may be sufficient to bring the mixture to the desired pH range.

[0302] The aqueous vehicle may also contain a buffering agent to stabilise the pH. When used, the buffer is selected from the group consisting of a phosphate buffer (such as sodium dihydrogen phosphate and disodium hydrogen phosphate), a borate buffer (such as boric acid, or salts thereof including disodium tetraborate), a citrate buffer (such as citric acid, or salts thereof including sodium citrate), and ϵ -aminocaproic acid, and mixtures thereof.

[0303] The formulation may further comprise a wetting agent. Suitable classes of wetting agents include those selected from the group consisting of polyoxypropylene-polyoxyethylene block copolymers (poloxamers), polyethoxylated ethers of castor oils, polyoxyethylenated sorbitan esters (polysorbates), polymers of oxyethylated octyl phenol (Tyloxapol), polyoxyl 40 stearate, fatty acid glycol esters, fatty acid glyceryl esters, sucrose fatty esters, and polyoxyethylene fatty esters, and mixtures thereof.

[0304] Oral compositions generally include an inert diluent or an edible pharmaceutically acceptable carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavouring agent such as peppermint, methyl salicylate, or orange flavoring.

[0305] According to a further aspect of the disclosure there is provided a pharmaceutical composition which comprises a compound of the disclosure as defined hereinbefore, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in association with a pharmaceutically acceptable diluent or carrier.

[0306] The compositions of the disclosure may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular, intraperitoneal or intramuscular dosing or as a suppository for rectal dosing).

[0307] The compositions of the disclosure may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

[0308] An effective amount of a compound of the present disclosure for use in therapy is an amount sufficient to treat or prevent an inflammasome related condition referred to herein, slow its progression and/or reduce the symptoms associated with the condition.

[0309] The size of the dose for therapeutic or prophylactic purposes of a compound of Formula (I) will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well-known principles of medicine.

Methods of Use

[0310] In some aspects, the present disclosure provides a method of inhibiting inflammasome (e.g., the NLRP3 inflammasome) activity (e.g., *in vitro* or *in vivo*), comprising contacting a cell with an effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof.

[0311] In some aspects, the present disclosure provides a method of treating or preventing a disease or disorder disclosed herein in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

[0312] In some embodiments, the disease or disorder is associated with an implicated inflammasome activity. In some embodiments, the disease or disorder is a disease or disorder in which inflammasome activity is implicated.

[0313] In some embodiments, the disease or disorder is an inflammatory disorder, autoinflammatory disorder, an autoimmune disorder, a neurodegenerative disease, or cancer.

[0314] In some embodiments, the disease or disorder is an inflammatory disorder, autoinflammatory disorder and/or an autoimmune disorder.

[0315] In some embodiments, the disease or disorder is cytokine release syndrome (CRS).

[0316] In some embodiments, the disease or disorder is selected from cryopyrin-associated autoinflammatory syndrome (CAPS; e.g., familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), chronic infantile neurological cutaneous and articular (CINCA) syndrome/ neonatal-onset multisystem inflammatory disease (NOMID)), familial Mediterranean fever (FMF), nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), gout, rheumatoid arthritis, osteoarthritis, Crohn's disease, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), fibrosis, obesity, type 2 diabetes, multiple sclerosis, dermatological disease (e.g. acne) and neuroinflammation occurring in protein misfolding diseases (e.g., Prion diseases).

[0317] In some embodiments, the disease or disorder is a neurodegenerative disease.

[0318] In some embodiments, the disease or disorder is Parkinson's disease or Alzheimer's disease.

[0319] In some embodiments, the disease or disorder is a dermatological disease.

[0320] In some embodiments, the dermatological disease is acne.

[0321] In some embodiments, the disease or disorder is cancer.

[0322] In some embodiments, the cancer is metastasising cancer, gastrointestinal cancer, skin cancer, non-small-cell lung carcinoma, brain cancer (e.g. glioblastoma) or colorectal adenocarcinoma.

[0323] In some embodiments, the cancer is breast cancer.

[0324] In some aspects, the present disclosure provides a method of treating or preventing an autoinflammatory disorder, an autoimmune disorder, a neurodegenerative disease or cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount

of a compound of the present disclosure or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

[0325] In some aspects, the present disclosure provides a method of treating or preventing an inflammatory disorder, autoinflammatory disorder and/or an autoimmune disorder selected from cryopyrin-associated autoinflammatory syndrome (CAPS; e.g., familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), chronic infantile neurological cutaneous and articular (CINCA) syndrome/ neonatal-onset multisystem inflammatory disease (NOMID)), familial Mediterranean fever (FMF), nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), gout, rheumatoid arthritis, osteoarthritis, Crohn's disease, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), fibrosis, obesity, type 2 diabetes, multiple sclerosis, dermatological disease (e.g. acne) and neuroinflammation occurring in protein misfolding diseases (e.g., Prion diseases) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

[0326] In some aspects, the present disclosure provides a method of treating or preventing cytokine release syndrome (CRS) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

[0327] In some embodiments, the CRS is associated with COVID-19. In some embodiments, the CRS is associated with adoptive cell therapy.

[0328] In some aspects, the present disclosure provides a method of treating or preventing a neurodegenerative disease (e.g., Parkinson's disease or Alzheimer's disease) in a subject in need thereof, said method comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

[0329] In some aspects, the present disclosure provides a method of treating or preventing cancer in a subject in need thereof, said method comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

[0330] In some aspects, the present disclosure provides a compound of the present disclosure or a pharmaceutically acceptable salt thereof for use in inhibiting inflammasome (e.g., the NLRP3 inflammasome) activity (e.g., *in vitro* or *in vivo*).

[0331] In some aspects, the present disclosure provides a compound of the present disclosure or a pharmaceutically acceptable salt thereof for use in treating or preventing a disease or disorder disclosed herein.

[0332] In some aspects, the present disclosure provides a compound of the present disclosure or a pharmaceutically acceptable salt thereof for use in treating or preventing an inflammatory disorder, an autoinflammatory disorder, an autoimmune disorder, a neurodegenerative disease or cancer in a subject in need thereof.

[0333] In some aspects, the present disclosure provides a compound of the present disclosure or a pharmaceutically acceptable salt thereof for use in treating or preventing an inflammatory disorder, an autoinflammatory disorder and/or an autoimmune disorder selected from cryopyrin-associated autoinflammatory syndrome (CAPS; e.g., familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), chronic infantile neurological cutaneous and articular (CINCA) syndrome/ neonatal-onset multisystem inflammatory disease (NOMID)), familial Mediterranean fever (FMF), nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), gout, rheumatoid arthritis, osteoarthritis, Crohn's disease, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), fibrosis, obesity, type 2 diabetes, multiple sclerosis and neuroinflammation occurring in protein misfolding diseases (e.g., Prion diseases) in a subject in need thereof.

[0334] In some aspects, the present disclosure provides a compound of the present disclosure or a pharmaceutically acceptable salt thereof for use in treating or preventing CRS in a subject in need thereof.

[0335] In some aspects, the present disclosure provides a compound of the present disclosure or a pharmaceutically acceptable salt thereof for use in treating or preventing a neurodegenerative disease (e.g., Parkinson's disease or Alzheimer's disease) in a subject in need thereof.

[0336] In some aspects, the present disclosure provides a compound of the present disclosure or a pharmaceutically acceptable salt thereof for use in treating or preventing cancer in a subject in need thereof.

[0337] In some aspects, the present disclosure provides use of a compound of the present disclosure or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for inhibiting inflammasome (e.g., the NLRP3 inflammasome) activity (e.g., *in vitro* or *in vivo*).

[0338] In some aspects, the present disclosure provides use of a compound of the present disclosure or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing a disease or disorder disclosed herein.

[0339] In some aspects, the present disclosure provides use of a compound of the present disclosure or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing an inflammatory disorder, an autoinflammatory disorder, an autoimmune disorder, a neurodegenerative disease or cancer in a subject in need thereof.

[0340] In some aspects, the present disclosure provides use of a compound of the present disclosure or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing an inflammatory disorder, an autoinflammatory disorder and/or an autoimmune disorder selected from cryopyrin-associated autoinflammatory syndrome (CAPS; e.g., familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), chronic infantile neurological cutaneous and articular (CINCA) syndrome/ neonatal-onset multisystem inflammatory disease (NOMID)), familial Mediterranean fever (FMF), nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), gout, rheumatoid arthritis, osteoarthritis, Crohn's disease, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), fibrosis, obesity, type 2 diabetes, multiple sclerosis, dermatological disorders (e.g., acne) and neuroinflammation occurring in protein misfolding diseases (e.g., Prion diseases) in a subject in need thereof.

[0341] In some aspects, the present disclosure provides use of a compound of the present disclosure or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing CRS in a subject in need thereof.

[0342] In some aspects, the present disclosure provides use of a compound of the present disclosure or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing a neurodegenerative disease (e.g., Parkinson's disease or Alzheimer's disease) in a subject in need thereof.

[0343] In some aspects, the present disclosure provides use of a compound of the present disclosure or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing cancer in a subject in need thereof.

[0344] The present disclosure provides compounds that function as inhibitors of inflammasome activity. The present disclosure therefore provides a method of inhibiting inflammasome activity *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as defined herein.

[0345] Effectiveness of compounds of the disclosure can be determined by industry-accepted assays/ disease models according to standard practices of elucidating the same as described in the art and are found in the current general knowledge.

[0346] The present disclosure also provides a method of treating a disease or disorder in which inflammasome activity is implicated in a patient in need of such treatment, said method comprising administering to said patient a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

[0347] On a general level, the compounds of the present disclosure, which inhibit the maturation of cytokines of the IL-1 family, are effective in all therapeutic indications that are mediated or associated with elevated levels of active forms of cytokines belonging to IL-1 family of cytokines (Sims J. et al. Nature Reviews Immunology 10, 89-102 (February 2010)).

[0348] Exemplary diseases and the corresponding references will be given in the following: inflammatory, autoinflammatory and autoimmune diseases like CAPS (Dinarello, C. A. Immunity. 2004 Mar;20(3):243-4; Hoffman, H. M. et al. Reumatologia 2005; 21(3)), gout, rheumatoid arthritis (Gabay, C. et al. Arthritis Research & Therapy 2009, 11:230; Schett, G. et al. Nat Rev Rheumatol. 2016 Jan;12(1):14-24.), Crohn's disease (Jung Mogg Kim Korean J. Gastroenterol. Vol. 58 No. 6, 300-310), COPD (Mortaz, E. et al. Tanaffos. 2011; 10(2): 9-14.), fibrosis (Gasse, P. et al. Am. J. Respir. Crit. Care Med. 2009 May 15;179(10):903-13), obesity, type 2 diabetes ((Dinarello, C. A. et al. Curr. Opin. Endocrinol. Diabetes Obes. 2010 Aug;17(4):314-21)) multiple sclerosis (see EAE-model in Coll, R. C. et al. Nat. Med. 2015 Mar;21(3):248-55) and many others (Martinon, F. et al. Immunol. 2009. 27:229-65) like Parkinson's disease or Alzheimer's disease (Michael, T. et al. Nature 493, 674-678 (31 January 2013); Halle, A. et al., Nat. Immunol. 2008 Aug;9(8):857-65; Saresella, M. et al. Mol. Neurodegener. 2016 Mar 3;11:23) and some oncological disorders.

[0349] Suitably, the compounds according to the present disclosure can be used for the treatment of a disease selected from the group consisting of cytokine release syndrome (CRS), an inflammatory disease, an autoinflammatory disease, an autoimmune disease, a neurodegenerative disease and cancer. Said inflammatory, autoinflammatory and autoimmune disease is suitably selected from the group consisting of a cryopyrin-associated autoinflammatory syndrome (CAPS, such as for example familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), chronic infantile neurological cutaneous and articular (CINCA) syndrome/ neonatal-onset multisystem inflammatory disease (NOMID)), familial Mediterranean fever (FMF), nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), chronic kidney disease (CKD), gout, rheumatoid arthritis, osteoarthritis, Crohn's disease, COPD, fibrosis, obesity, type 2 diabetes, multiple sclerosis, dermatological diseases (e.g., acne) and neuroinflammation occurring in protein misfolding diseases, such as Prion diseases. Said neurodegenerative disease includes, but is not limited, to Parkinson's disease and Alzheimer's disease.

[0350] Accordingly, the compounds of the present disclosure can be used for the treatment of a disease selected from the group consisting of cryopyrin-associated autoinflammatory syndrome (CAPS, such as for example familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), chronic infantile neurological cutaneous and articular (CINCA) syndrome/ neonatal-onset multisystem inflammatory disease (NOMID)), familial Mediterranean fever (FMF), nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), chronic kidney disease (CKD), gout, rheumatoid arthritis, osteoarthritis, Crohn's disease, COPD, fibrosis, obesity, type 2 diabetes, multiple sclerosis, dermatological diseases (e.g., acne) neuroinflammation occurring in protein misfolding diseases, such as Prion diseases, neurodegenerative diseases (e.g., Parkinson's disease, Alzheimer's disease) and oncological disorders.

Inflammatory Disease Associated with Infection

[0351] In some embodiments, the disease or disorder is an inflammatory disease.

[0352] In some embodiments, the inflammatory disease is associated with an infection.

[0353] In some embodiments, the inflammatory disease is associated with an infection by a virus.

[0354] In some embodiments, the inflammatory disease is associated with an infection by an RNA virus. In some embodiments, the RNA virus is a single stranded RNA virus. Single stranded RNA

viruses include group IV (positive strand) and group V (negative strand) single stranded RNA viruses. In some embodiments, Group IV viruses include coronaviruses.

[0355] In some embodiments, the inflammatory disease is associated with an infection by a coronavirus. In some embodiments, the coronavirus is Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV 2), SARS coronavirus (SARS CoV) or Middle East respiratory syndrome-related coronavirus (MERS).

[0356] In some embodiments, the inflammatory disease is associated with an infection by SARS-CoV 2. In some embodiments, the SARS-CoV 2 infection leads to the 2019 novel coronavirus disease (COVID-19). In some embodiments, the SARS-CoV 2 infection leads to a novel variant of the 2019 novel coronavirus disease (COVID-19).

[0357] In some embodiments, the inflammatory disease is an inflammatory disease of the lung.

[0358] In some embodiments, the inflammatory disease of the lung is associated with an infection by SARS-CoV 2.

[0359] In some embodiments, the inflammatory disease comprises cytokine release syndrome (CRS).

[0360] In some embodiments, the cytokine release syndrome (CRS) is associated with an infection by SARS-CoV 2.

[0361] In some embodiments, the cytokine release syndrome (CRS) is associated with an infection by a variant of SARS-CoV 2.

[0362] In some embodiments, a variant of SARS-CoV 2 is the mutated SARS-CoV 2 infection leads to a novel variant of the 2019 novel coronavirus disease (COVID-19).

Cytokine Release Syndrome and Immunotherapy

[0363] In some embodiments, the disease or disorder is an inflammatory disease.

[0364] In some embodiments, the inflammatory disease is associated with an immunotherapy.

[0365] In some embodiments, the immunotherapy causes cytokine release syndrome (CRS).

[0366] The effectiveness of immunotherapies, such as CAR-T, are hampered by the frequency with which such therapies induce cytokine release syndrome. Without wishing to be bound by theory, it is thought that the severity of CRS induced by immunotherapy is mediated by IL-6, IL-1 and NO production (Giavridis et al. *Nature Medicine* **24**, 731-738 (2018)). Alternatively, or in addition, CRS may occur when cells targeted by the adoptive cell therapy undergo pyroptosis, a

highly inflammatory form of programmed cell death. Pyroptosis leads to release of factors that stimulate macrophages to produce pro-inflammatory cytokines, leading to CRS (Liu et al. *Science Immunology* 5, eaax7969 (2020)).

[0367] In some embodiments, the immunotherapy comprises an antibody or an adoptive cell therapy.

[0368] In some embodiments, the adoptive cell therapy comprises a CAR-T or TCR-T cell therapy.

[0369] In some embodiments, the adoptive cell therapy comprises a cancer therapy. In some embodiments, the cancer therapy is a treatment of B cell lymphoma or B cell acute lymphoblastic leukemia. In some embodiments, the adoptive cells may express a CAR targeting CD19+ B cell acute lymphoblastic leukemia cells.

[0370] In some embodiments, the adoptive cell therapy comprises administration of T cells, B cells, or NK cells.

[0371] In some embodiments, the adoptive cell therapy comprises administration of T cells. In some embodiments, the adoptive cell therapy comprises administration of B cells. In some embodiments, the adoptive cell therapy comprises administration of NK cells.

[0372] In some embodiments, the adoptive cell therapy is autologous.

[0373] In some embodiments, the adoptive therapy is allogeneic.

Treatment in Cancer; Links with Inflammasome

[0374] Chronic inflammation responses have long been observed to be associated with various types of cancer. During malignant transformation or cancer therapy inflammasomes may become activated in response to danger signals and this activation may be both beneficial and detrimental in cancer.

[0375] IL-1 β expression is elevated in a variety of cancers (including breast, prostate, colon, lung, head and neck cancers and melanomas) and patients with IL-1 β producing tumours generally have a worse prognosis (Lewis, Anne M., et al. "Interleukin-1 and cancer progression: the emerging role of interleukin-1 receptor antagonist as a novel therapeutic agent in cancer treatment." *Journal of translational medicine* 4.1 (2006): 48).

[0376] Cancers derived from epithelial cells (carcinoma) or epithelium in glands (adenocarcinoma) are heterogeneous; consisting of many different cell types. This may include

fibroblasts, immune cells, adipocytes, endothelial cells and pericytes amongst others, all of which may be cytokine/ chemokine secreting (Grivennikov, Sergei I., Florian R. Greten, and Michael Karin. "Immunity, inflammation, and cancer." *Cell* 140.6 (2010): 883-899). This can lead to cancer-associated inflammation through the immune cell infiltration. The presence of leukocytes in tumours is known but it has only recently become evident that an inflammatory microenvironment is an essential component of all tumours. Most tumours (>90%) are the result of somatic mutations or environmental factors rather than germline mutations and many environmental causes of cancer are associated with chronic inflammation (20% of cancers are related to chronic infection, 30% to smoking/ inhaled pollutants and 35% to dietary factors (20% of all cancers are linked to obesity) (Aggarwal, Bharat B., R. V. Vijayalekshmi, and Bokyoung Sung. "Targeting inflammatory pathways for prevention and therapy of cancer: short-term friend, long-term foe." *Clinical Cancer Research* 15.2 (2009): 425-430).

GI Cancers

[0377] Cancers of the gastrointestinal (GI) tract are frequently associated with chronic inflammation. For example, *H. pylori* infection is associated with gastric cancer (Amieva, Manuel, and Richard M. Peek. "Pathobiology of *Helicobacter pylori*-Induced Gastric Cancer." *Gastroenterology* 150.1 (2016): 64-78). Colorectal cancer is associated with inflammatory bowel disease (Bernstein, Charles N., et al. "Cancer risk in patients with inflammatory bowel disease." *Cancer* 91.4 (2001): 854-862). Chronic inflammation in stomach leads to the upregulation of IL-1 and other cytokines (Basso, D. et al., (1996) *Helicobacter pylori* infection enhances mucosal interleukin-1 beta, interleukin-6, and the soluble receptor of interleukin-2. *Int J Clin Lab Res* 26:207-210) and polymorphisms in IL-1 β gene can increase risk of gastric cancer (Wang, P. et al., (2007) Association of interleukin-1 gene polymorphisms with gastric cancer: a meta-analysis. *Int J Cancer* 120:552-562).

[0378] In 19 % of gastric cancer cases, caspase-1 expression is decreased which correlates with stage, lymph node metastasis and survival (Jee et al., 2005). *Mycoplasma hyorhinis* is associated with the development of gastric cancer its activation of the NLRP3 inflammasome may be associated with its promotion of gastric cancer metastasis (Xu et al., 2013).

Skin Cancers

[0379] Ultraviolet radiation is the greatest environmental risk for skin cancer which is promoted by causing DNA damage, immunosuppression and inflammation. The most malignant skin cancer, melanoma, is characterised by the upregulation of inflammatory cytokines, all of which can be regulated by IL-1 β (Lázár-Molnár, Eszter, et al. "Autocrine and paracrine regulation by cytokines and growth factors in melanoma." *Cytokine* 12.6 (2000): 547-554). Systemic inflammation induces an enhancement of melanoma cell metastasis and growth by IL-1-dependent mechanisms in vivo. Using thymoquinone inhibition of metastasis in a B16F10 mouse melanoma model was shown to be dependent on inhibition of the NLRP3 inflammasome (Ahmad, Israr, et al. "Thymoquinone suppresses metastasis of melanoma cells by inhibition of NLRP3 inflammasome." *Toxicology and applied pharmacology* 270.1 (2013): 70-76).

Glioblastoma

[0380] NLRP3 contributes to radiotherapy resistance in glioma. Ionising radiation can induce NLRP3 expression whereas NLRP3 inhibition reduced tumour growth and prolonged mouse survival following radiation therapy. NLRP3 inflammasome inhibition can therefore provide a therapeutic strategy for radiation-resistant glioma (Li, Lianling, and Yuguang Liu. "Aging-related gene signature regulated by Nlrp3 predicts glioma progression." *American journal of cancer research* 5.1 (2015): 442).

Metastasis

[0381] More widely, NLRP3 is considered by the applicants to be involved in the promotion of metastasis and consequently modulation of NLRP3 should plausibly block this. IL-1 is involved in tumour genesis, tumour invasiveness, metastasis, tumour host interactions (Apte, Ron N., et al. "The involvement of IL-1 in tumorigenesis, tumour invasiveness, metastasis and tumour-host interactions." *Cancer and Metastasis Reviews* 25.3 (2006): 387-408) and angiogenesis (Voronov, Elena, et al. "IL-1 is required for tumor invasiveness and angiogenesis." *Proceedings of the National Academy of Sciences* 100.5 (2003): 2645-2650).

[0382] The IL-1 gene is frequently expressed in metastases from patients with several types of human cancers. For example, IL-1mRNA was highly expressed in more than half of all tested metastatic human tumour specimens including specifically non-small-cell lung carcinoma, colorectal adenocarcinoma, and melanoma tumour samples (Elaraj, Dina M., et al. "The role of

interleukin 1 in growth and metastasis of human cancer xenografts." *Clinical Cancer Research* 12.4 (2006): 1088-1096) and IL-1RA inhibits xenograft growth in IL-1 producing tumours but without anti-proliferative effects in vitro.

[0383] Further, IL-1 signalling is a biomarker for predicting breast cancer patients at increased risk for developing bone metastasis. In mouse models IL-1 β and its receptor are upregulated in breast cancer cells that metastasise to bone compared with cells that do not. In a mouse model the IL-1 receptor antagonist anakinra reduced proliferation and angiogenesis in addition to exerting significant effects on the tumour environment reducing bone turnover markers, IL-1 β and TNF alpha (Holen, Ingunn, et al. "IL-1 drives breast cancer growth and bone metastasis in vivo." *Oncotarget* (2016).

[0384] IL-18 induced the production of MMP-9 in the human leukaemia cell line HL-60, thus favouring degradation of the extracellular matrix and the migration and invasiveness of cancer cells (Zhang, Bin, et al. "IL-18 increases invasiveness of HL-60 myeloid leukemia cells: up-regulation of matrix metalloproteinases-9 (MMP-9) expression." *Leukemia research* 28.1 (2004): 91-95). Additionally IL-18 can support the development of tumour metastasis in the liver by inducing expression of VCAM-1 on hepatic sinusoidal endothelium (Carrascal, Maria Teresa, et al. "Interleukin-18 binding protein reduces b16 melanoma hepatic metastasis by neutralizing adhesiveness and growth factors of sinusoidal endothelium." *Cancer Research* 63.2 (2003): 491-497).

CD36

[0385] The fatty acid scavenger receptor CD36 serves a dual role in priming gene transcription of pro-IL-1 β and inducing assembly of the NLRP3 inflammasome complex. CD36 and the TLR4-TLR6 heterodimer recognise oxLDL, which initiates a signalling pathway leading to transcriptional upregulation of NLRP3 and pro-IL-1 β (signal 1). CD36 also mediates the internalisation of oxLDL into the lysosomal compartment, where crystals are formed that induce lysosomal rupture and activation of the NLRP3 inflammasome (signal 2) (Kagan, J. and Horng T., "NLRP3 inflammasome activation: CD36 serves double duty." *Nature immunology* 14.8 (2013): 772-774).

[0386] A subpopulation of human oral carcinoma cells express high levels of the fatty acid scavenger receptor CD36 and are unique in their ability to initiate metastasis. Palmitic acid or a

high fat diet boosted the metastatic potential of the CD36⁺ cells. Neutralising anti-CD36 antibodies blocked metastasis in orthotopic mouse models of human oral cancer. The presence of CD36⁺ metastasis-initiating cells correlates with a poor prognosis for numerous types of carcinomas. It is suggested that dietary lipids may promote metastasis (Pasqual, G, Avgustinova, A., Mejetta, S, Martin, M, Castellanos, A, Attolini, CS-O, Berenguer, A., Prats, N, Toll, A, Hueto, JA, Bescos, C, Di Croce, L, and Benitah, SA. 2017 "Targeting metastasis-initiating cells through the fatty acid receptor CD36" Nature 541:41-45).

[0387] In hepatocellular carcinoma exogenous palmitic acid activated an epithelial-mesenchymal transition (EMT)-like program and induced migration that was decreased by the CD36 inhibitor, sulpho-N-succinimidyl oleate (Nath, Aritro, et al. "Elevated free fatty acid uptake via CD36 promotes epithelial-mesenchymal transition in hepatocellular carcinoma." Scientific reports 5 (2015). Body mass index was not associated with the degree of EMT highlighting that it is actually CD36 and free fatty acids that are important.

[0388] Cancer stems cells (CSCs) use CD36 to promote their maintenance. Oxidised phospholipids, ligands of CD36, were present in glioblastoma and the proliferation of CSCs but not non-CSCs increased with exposure to oxidised LDL. CD36 also correlated with patient prognosis.

Chemotherapy Resistance

[0389] In addition to direct cytotoxic effects, chemotherapeutic agents harness the host immune system which contributes to anti-tumour activity. However, gemcitabine and 5-FU were shown to activate NLRP3 in myeloid-derived suppressor cells leading to production of IL-1 β which curtails anti-tumour efficacy. Mechanistically these agents destabilised the lysosome to release cathepsin B to activate NLRP3. IL-1 β drove the production of IL-17 from CD4⁺ T cells, which in turn blunted the efficacy of the chemotherapy. Higher anti-tumoral effects for both gemcitabine and 5-FU were observed when tumours were established in NLRP3^{-/-} or Caps1^{-/-} mice, or WT mice treated with IL-1RA. Myeloid-derived suppressor cell NLRP3 activation therefore limits the anti-tumour efficacy of gemcitabine and 5-FU (Bruchard, Mélanie, et al. "Chemotherapy-triggered cathepsin B release in myeloid-derived suppressor cells activates the Nlrp3 inflammasome and promotes tumour growth." Nature medicine 19.1 (2013): 57-64.). Compounds of the present disclosure may therefore be useful in chemotherapy to treat a range of cancers.

[0390] Compounds of the present disclosure, or pharmaceutically acceptable salts thereof, may be administered alone as a sole therapy or can be administered in addition with one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment.

[0391] For example, therapeutic effectiveness may be enhanced by administration of an adjuvant (i.e. by itself the adjuvant may only have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the individual is enhanced). Alternatively, by way of example only, the benefit experienced by an individual may be increased by administering the compound of Formula (I) with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit.

[0392] In the instances where the compound of the present disclosure is administered in combination with other therapeutic agents, the compound of the disclosure need not be administered via the same route as other therapeutic agents, and may, because of different physical and chemical characteristics, be administered by a different route. For example, the compound of the disclosure may be administered orally to generate and maintain good blood levels thereof, while the other therapeutic agent may be administered intravenously. The initial administration may be made according to established protocols known in the art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician.

[0393] The particular choice of other therapeutic agent will depend upon the diagnosis of the attending physicians and their judgment of the condition of the individual and the appropriate treatment protocol. According to this aspect of the disclosure there is provided a combination for use in the treatment of a disease in which inflammasome activity is implicated comprising a compound of the disclosure as defined hereinbefore, or a pharmaceutically acceptable salt thereof, and another suitable agent.

[0394] According to a further aspect of the disclosure there is provided a pharmaceutical composition which comprises a compound of the disclosure, or a pharmaceutically acceptable salt thereof, in combination with a suitable, in association with a pharmaceutically acceptable diluent or carrier.

[0395] In addition to its use in therapeutic medicine, compounds of Formula (I) and pharmaceutically acceptable salts thereof are also useful as pharmacological tools in the

development and standardisation of in vitro and in vivo test systems for the evaluation of the effects of inhibitors of inflammasome in laboratory animals such as dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

[0396] In any of the above-mentioned pharmaceutical composition, process, method, use, medicament, and manufacturing features of the instant disclosure, any of the alternate embodiments of macromolecules of the present disclosure described herein also apply.

Routes of Administration

[0397] The compounds of the disclosure or pharmaceutical compositions comprising these compounds may be administered to a subject by any convenient route of administration, whether systemically/ peripherally or topically (i.e., at the site of desired action).

[0398] Routes of administration include, but are not limited to, oral (e.g. by ingestion); buccal; sublingual; transdermal (including, e.g., by a patch, plaster, etc.); transmucosal (including, e.g., by a patch, plaster, etc.); intranasal (e.g., by nasal spray); ocular (e.g., by eye drops); pulmonary (e.g., by inhalation or insufflation therapy using, e.g., via an aerosol, e.g., through the mouth or nose); rectal (e.g., by suppository or enema); vaginal (e.g., by pessary); parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intra-arterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal; by implant of a depot or reservoir, for example, subcutaneously or intramuscularly.

EXAMPLES

[0399] For exemplary purpose, salts of the compounds of Formula (I) are synthesized and tested in the examples. It is understood that neutral compounds of Formula (I) may be similarly synthesized and tested using the exemplary procedures described in the examples. Further, it is understood that the salts (e.g., sodium salt) of the compounds of Formula (I) may be converted to the corresponding neutral compounds using routine techniques in the art (e.g., pH adjustment and, optionally, extraction (e.g., into an aqueous phase)).

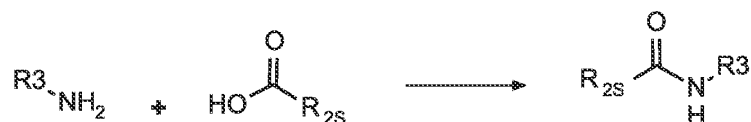
[0400] Nuclear magnetic resonance (NMR) spectra were recorded at 400 MHz or 300 MHz as stated and at 300.3 K unless otherwise stated; the chemical shifts (δ) are reported in parts per million (ppm). Spectra were recorded using a Bruker or Varian instrument with 8, 16 or 32 scans.

[0401] LC-MS chromatograms and spectra were recorded using an Agilent 1200 or Shimadzu LC-20 AD&MS 2020 instrument using a C-18 column such as a Luna-C18 2.0x30 mm or Xbridge Shield RPC18 2.1x50 mm. Injection volumes were 0.7 – 8.0 μ L and the flow rates were typically 0.8 or 1.2 mL/min. Detection methods were diode array (DAD) or evaporative light scattering (ELSD) as well as positive ion electrospray ionisation. MS range was 100 - 1000 Da. Solvents were gradients of water and acetonitrile both containing a modifier (typically 0.01 – 0.04 %) such as trifluoroacetic acid or ammonium carbonate.

[0402] Abbreviations:

ACN	Acetonitrile
AcOH	Acetic acid
aq.	Aqueous
DCM	Dichloromethane
DMF	N,N-dimethylformamide
DMSO- <i>d</i> ₆	Hexadeuterodimethylsulfoxide
eq.	Equivalents
MS ES ⁺	Positive ion electrospray ionisation mass spectroscopy
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ESI	Electrospray ionisation
EtOAc	Ethyl acetate
FCC	Flash column chromatography
h	Hour(s)
HATU	N-[(Dimethylamino)-1H-1,2,3-triazolo-[4,5-b]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide
HPLC	High performance liquid chromatography
LC-MS	Liquid chromatography-mass spectrometry
MeOD	Methanol- <i>d</i> ₄
MeOH	Methanol
Min	Minute(s)
MTBE	Methyl tert-butylether

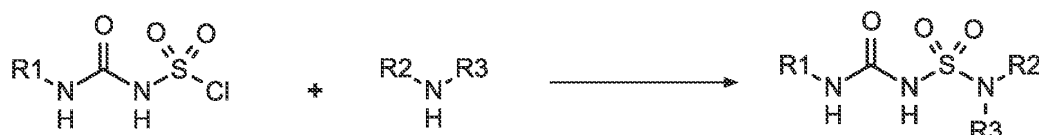
RM	Reaction mixture
Rt	Room temperature
sat.	Saturated
SM	Starting material
T ₃ P	Propylphosphonic anhydride
TBSCl	Tert-butyldimethylsilyl chloride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Y	Yield

General Procedure A

[0403] To a solution of a carboxylic acid (1 eq) in DMF (0.9 M) was added HATU (1.2 eq) and the solution was stirred at 0° C for 1 h. Amine (1.1 eq) and DIPEA (2 eq) were added and the RM stirred at 0° C for 2 h. The RM was quenched (water) and the mixture extracted (EtOAc). The combined organic layers were washed (brine), dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified by column chromatography.

General Procedure B

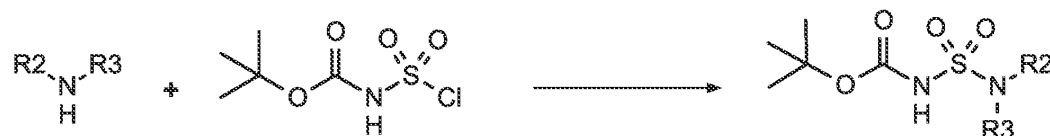
[0404] To a solution of amide (1 eq) in THF (1M) was added LiAlH₄ (10 eq) at 0° C and stirred for 20 min under N₂. The mixture was stirred at 70° C for 1 h under N₂. The RM was quenched (H₂O and aqueous NaOH) at 0° C. The mixture was filtered and the filtrate concentrated *in vacuo* to afford the desired product.

General procedure C

[0405] To a solution of sulfamoyl chloride (1 eq) and amine (1 eq) in THF (0.2 M) was added NaOH (1 eq) or NaH (4 eq) at 0° C under N₂. The mixture was stirred at 0° C for 2 h. The reaction was evaporated under flow of N₂.

General procedure D

[0406] To a solution of chlorosulfonyl isocyanate (1 eq) in isopropyl ether (0.4 M) cooled to -30° C under nitrogen was added amine (1 eq) in isopropyl ether (0.4 M). The RM was stirred at -30° C for between 0.5 and 2 h and monitored by LC-MS (for appearance of methyl sulfonate). The product was used directly as a solution in isopropyl ether (0.2 M).

General Procedure E

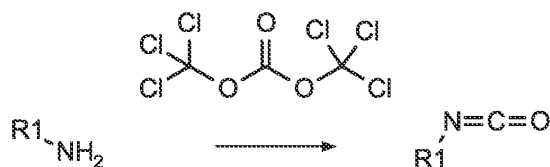
[0407] To a solution of amine (1 eq) in THF (0.5 M) was added DIPEA (2 eq) and tert-butyl N-chlorosulfonylcarbamate (INT-C) (1.5 eq) at 0° C. The mixture was stirred at 0° C for 1 h. The reaction mixture was concentrated *in vacuo*. The residue was diluted (H₂O). The mixture was extracted (EtOAc x 3). The combined organic layers were washed (brine), dried (Na₂SO₄) and concentrated *in vacuo*.

General Procedure F

[0408] A mixture of the tert-butyl sulfamoyl carbamate (1 eq) and 4 M HCl in EtOAc (0.2 M) was stirred at 25° C for 1 h. The RM was filtered and the filter cake dissolved in H₂O at 25° C. An aqueous solution of Na₂CO₃ was added dropwise at 25° C until some solid precipitated out and the pH reached 8. After 10 mins, THF was added to dissolve the precipitate. The solution was dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give the title compound as a free base.

General Procedure G

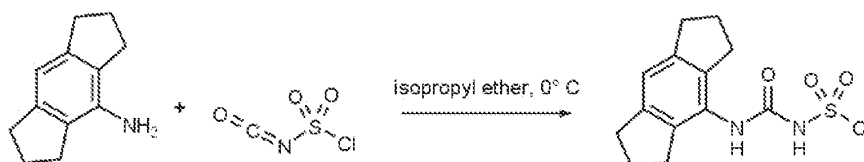
[0409] To a solution of the sulfamoyl amine (1 eq) and the isocyanate (1 eq) in THF (0.23 M) was added NaOH (1 eq) at 0° C. The mixture was stirred at 0° C for 12 h.

General procedure H

[0410] To a solution of amine (1 eq.) in dioxane (0.1 M) was added triphosgene (1.1 eq.) and a base. The RM was stirred at 40° C for 1 h or until complete. The solvent was removed in *vacuo* to give the desired product.

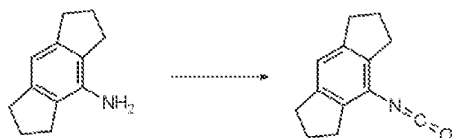
Synthesis of Intermediates

[0411] Intermediate A. {[(1,2,3,5,6,7-Hexahydro-s-indacen-4-yl)carbamoyl]amino}sulfonyl chloride.



[0412] For synthesis of 1,2,3,5,6,7-hexahydro-s-indacen-4-amine, patent application WO 9832733 A1 may be used as a direct reference. To a solution of chlorosulfonyl isocyanate (185 μ L, 2.13 mmol) in isopropyl ether (20 mL) was added 1,2,3,5,6,7-hexahydro-s-indacen-4-amine (369 mg, 2.13 mmol) at -15°C. The mixture was stirred at -15°C for 0.5 h. The reaction product was used directly in the next step. LC-MS in MeOH (ESI): m/z: [MH]⁺ = 311.

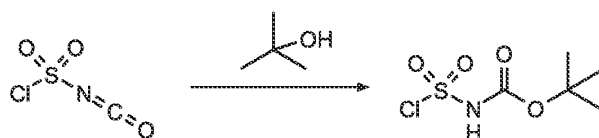
[0413] Intermediate B. 4-Isocyanato-1,2,3,5,6,7-hexahydro-s-indacene.



[0414] For synthesis of 1,2,3,5,6,7-hexahydro-s-indacen-4-amine see patent application WO 9832733 A1.

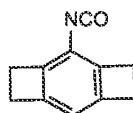
To a mixture of triphosgene (1.71 g, 5.77 mmol) in DCM (5 mL) cooled to 0°C under nitrogen was added portionwise 1,2,3,5,6,7-hexahydro-s-indacen-4-amine (1.00 g, 5.77 mmol) and triethylamine (1.69 mL, 12.12 mmol). The mixture was stirred at rt for 5 h. The mixture was concentrated under reduced pressure to give the title compound as a white solid. LC-MS in MeOH (ESI): m/z: [M+MeOH+H]⁺ = 232

[0415] Intermediate C. Tert-butyl N-(chlorosulfonyl)carbamate.



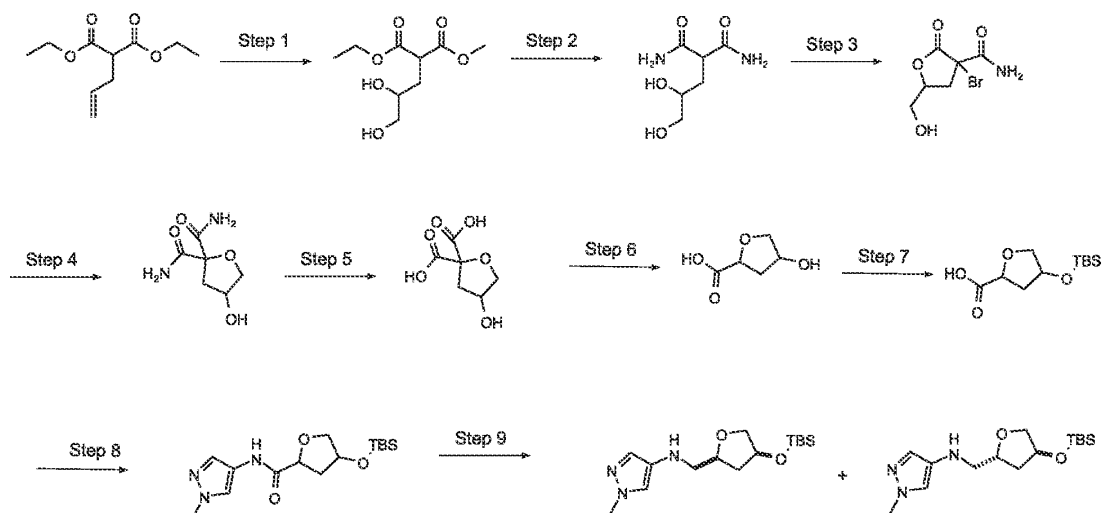
[0416] To a solution of N-(oxomethylene)sulfamoyl chloride (307 μ L, 3.53 mmol) in DCM (6 mL) cooled to 0° C was added a solution of tert-butanol (338 μ L, 3.53 mmol) in DCM (6 mL). The mixture was stirred at 0° C for 2 h. The solution was used directly in the next step.

[0417] Intermediate D. 2-Isocyanatotricyclo[6.2.0.0^{3,6}]deca-1,3(6),7-triene



The title compound was prepared as described in patent application WO 2019023147 A1 and was used immediately. Y = 98 %. LCMS in MeOH (ESI): m/z: [M+MeOH+H]⁺ = 204.0.

[0418] Intermediates E and F.



[0419] **Step 1. 1-Ethyl 3-methyl 2-(2,3-dihydroxypropyl)propanedioate.** To a solution of 1,3-diethyl 2-(prop-2-en-1-yl)propanedioate (52.5 mL, 265 mmol) in formic acid (239 mL) was added H₂O₂ (27.3 mL, 28 % solution, 265 mmol) at 0° C. The RM was stirred at 0° C for 0.5 h and 25° C for 23.5 h under N₂. The RM mixture was quenched by addition of sat. Na₂SO₃ until iodide-starch test paper indicated that all H₂O₂ was consumed. The RM was extracted (DCM, 3 x 100 mL). The combined organic phase was washed (brine, 50 mL), dried (Na₂SO₄) and concentrated *in vacuo* to give the title compound as a colourless oil. Y = 89 %. ¹H NMR (400 MHz, DMSO-*d*₆)

δ 8.29 (s, 1H), 8.27 (s, 1H), 4.93 - 4.87 (m, 1H), 4.82 - 4.71 (m, 1H), 4.46 - 4.30 (m, 2H), 4.29 - 4.22 (m, 2H), 4.03 - 3.86 (m, 2H), 2.61 - 2.53 (m, 1H), 2.38 - 2.30 (m, 1H), 1.24 - 1.19 (m, 6H).

[0420] **Step 2. 2-(2,3-Dihydroxypropyl)propanediamide.** To a solution of 1-ethyl 3-methyl 2-(2,3-dihydroxypropyl)propanedioate (54 g, 231 mmol) in EtOH (500 mL) was bubbled NH_3 (gas) at 0° C. The RM was stirred at 0° C for 1 h and filtered to afford the title compound as a white solid. Y = 86 %. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.26 - 7.12 (m, 2H), 7.06 - 6.93 (m, 2H), 4.52 - 4.41 (m, 2H), 3.34 - 3.28 (m, 1H), 3.27 - 3.18 (m, 3H), 1.95 - 1.88 (m, 1H), 1.52 - 1.45 (m, 1H)

[0421] **Step 3. 3-Bromo-5-(hydroxymethyl)-2-oxoxolane-3-carboxamide.** A solution of 2-(2,3-dihydroxypropyl)propanediamide (25 g, 142 mmol) in AcOH (500 mL) was stirred at 40° C for 2 h. Br_2 (7.32 mL, 41.9 mmol) was added at 0° C and stirred at 25° C for 26 h. The mixture was filtered, and the filtrate was concentrated *in vacuo* to give the title compound, used without further purification. ^1H NMR (400 MHz, MeOD) δ 4.78 - 4.70 (m, 1H), 3.91 (dd, J = 13, 3 Hz, 1H), 3.69 (dd, J = 13, 4 Hz, 1H), 2.95 (dd, J = 10, 15 Hz, 1H), 2.64 (dd, J = 5, 15 Hz, 1H)

[0422] **Step 4. 4-Hydroxyoxolane-2,2-dicarboxamide.** A solution of NH_3 was bubbled through a solution of 3-bromo-5-(hydroxymethyl)-2-oxo-tetrahydrofuran-3-carboxamide (33 g, 139 mmol) in EtOH (400 mL) at 0° C. The RM was stirred at 50° C for 6 h. The RM was filtered and the filter cake dried *in vacuo* to give the title compound as a white solid (Y = 79 %), which was used for the next step directly.

[0423] **Step 5 4-Hydroxyoxolane-2,2-dicarboxylic acid.** A mixture of 4-hydroxyoxolane-2,2-dicarboxamide (10 g, 57.4 mmol) and 6 M HCl (105 mL) was stirred at 50° C for 4 h under N_2 . The RM was concentrated *in vacuo* to give the title compound as a yellow solid, which was used for the next step directly.

[0424] **Step 6. 4-Hydroxyoxolane-2-carboxylic acid.** 4-Hydroxyoxolane-2,2-dicarboxylic acid (2.0 g, 11.36 mmol) in H_2O (12 mL) was heated at 150° C for 1.5 h using microwave heating in a sealed tube. A further four batches on the same scale were run in parallel. The reaction mixtures were combined and concentrated *in vacuo* to give the title compound as a white solid, used without further purification. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 4.43 - 4.37 (m, 1H), 4.34 - 4.28 (m, 2H), 4.28 - 4.23 (m, 1H), 3.81 - 3.73 (m, 3H), 3.65 - 3.59 (m, 3H), 2.35 - 2.23 (m, 1H), 2.12 - 2.02 (m, 1H), 2.00 - 1.86 (m, 2H).

[0425] **Step 7. 4-[(Tert-butyl dimethylsilyl)oxy]oxolane-2-carboxylic acid** To a solution of 4-hydroxytetrahydrofuran-2-carboxylic acid (10 g, 75.7 mmol) in THF (300 mL) cooled to 0° C was added TBSCl (18.6 mL, 151 mmol) and imidazole (25.8 g, 378 mmol). The RM was stirred at 25° C for 3 h. The RM was concentrated *in vacuo*. The residue was diluted (water, 300 mL) and the resulting mixture extracted (EtOAc, 3 x 100 mL). The combined organic layers were washed (brine, 100 mL), dried (Na₂SO₄) and concentrated *in vacuo* to give the title compound as a brown oil, used without further purification.

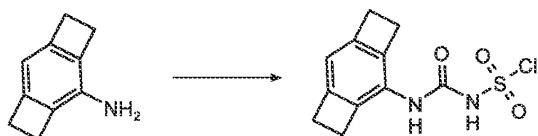
[0426] **Step 8. 4-[(Tert-butyl dimethylsilyl)oxy]-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide.** To a solution of 4 - [(tert - butyl dimethylsilyl)oxy]oxolane - 2 - carboxylic acid (6.3 g, 25.6 mmol) in DMF (60 mL) was added HATU (11.7 g, 30.7 mmol) at 0° C and stirred for 1 h, followed by DIPEA (8.91 mL, 51.1 mmol) and 1-methylpyrazol-4-amine (2.73 g, 28.1 mmol). The mixture was stirred at 0° C for 1 h. The reaction mixture was diluted (water, 100 mL) and the resulting mixture extracted (EtOAc, 3 x 100 mL). The combined organic layers were washed (brine, 100 mL), dried (Na₂SO₄) and concentrated *in vacuo* to give a brown oil. This was purified by FCC (SiO₂, 0 – 50 % EtOAc in pet. ether) to give the title compound as a yellow gum (Y = 6 %). ¹H NMR (400 MHz, MeOD) δ 7.90 (s, 1H), 7.89 (s, 1H), 7.57 (s, 1H), 7.56 (s, 1H), 4.64 - 4.58 (m, 2H), 4.53 - 4.46 (m, 2H), 4.13 - 4.07 (m, 1H), 4.04 - 3.98 (m, 1H), 3.93 - 3.88 (m, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.82 - 3.79 (m, 1H), 2.42 - 2.21 (m, 4H), 0.93 - 0.91 (m, 9H), 0.75 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H) (Note: two sets of signals).

[0427] **Step 9. Syn-N-[[4-[tert-butyl(dimethyl)silyl]oxytetrahydrofuran-2-yl]methyl]-1-methyl-pyrazol-4-amine and anti-N-[[4-[tert-butyl(dimethyl)silyl]oxytetrahydrofuran-2-yl]methyl]-1-methyl - pyrazol-4-amine.** A mixture of 4-[tert-butyl(dimethyl)silyl]oxy-N-(1-methylpyrazol-4-yl)tetrahydrofuran-2- carboxamide (400 mg, 1.23 mmol) and 1 M BH₃.THF (8.0 mL, 8.0 mmol) was stirred at 0° C for 0.5 h. The RM was heated to 80° C for 1 h. The RM was quenched (MeOH, 3 mL) at 0° C, and concentrated *in vacuo*. Prep-HPLC (column: Phenomenex Gemini-NX C18, 3 μm, 75 x 30 mm; mobile phase: [water (0.04 % NH₃H₂O + 10 mM NH₄HCO₃) - ACN]; B: 30 – 60 %, 10 min) gave syn-N-[[4-[tert-butyl(dimethyl)silyl]oxytetrahydrofuran-2 -yl]methyl]-1-methyl-pyrazol-4-amine (Y = 21 %) and anti-N-[[4-[tert-butyl(dimethyl)silyl]oxytetrahydrofuran-2-yl]methyl]-1-methyl - pyrazol-4-amine (Y = 18 %) as white solids. **Syn-N-[[4-[tert-butyl(dimethyl)silyl]oxytetrahydrofuran-2 -yl]methyl]-1-methyl-pyrazol-4-amine**

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 6.59 (s, 1H), 6.40 (s, 1H), 4.00 (t, $J = 7$ Hz, 1H), 3.65 - 3.62 (m, 1H), 3.17 - 3.12 (m, 1H), 2.94 (s, 3H), 2.90 - 2.84 (m, 1H), 2.77 - 2.72 (m, 1H), 2.18 - 2.14 (m, 2H), 1.43 - 1.34 (m, 1H), 0.75 - 0.70 (m, 1H), 0.04 (s, 9H), -0.76, -0.77 (2s, 6H). LC-MS (ESI): m/z : $[\text{M}+\text{H}] = 312.1$.

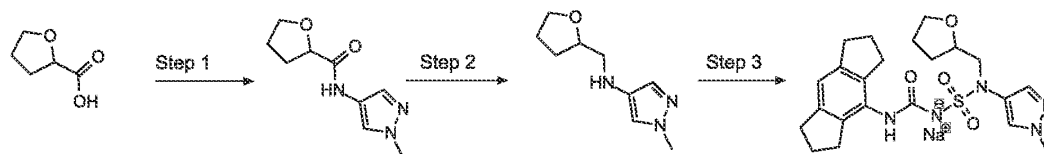
[0428] **Anti-N-[[4-[tert-butyl(dimethyl)silyl]oxytetrahydrofuran-2-yl]methyl]-1-methyl-pyrazol-4-amine** ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.42 (s, 1H), 7.23 (s, 1H), 4.80 (t, $J = 6$ Hz, 1H), 4.49 - 4.46 (m, 1H), 4.16 - 4.08 (m, 1H), 3.92 - 3.88 (m, 1H), 3.75 (s, 3H), 3.48 - 3.45 (m, 1H), 3.00 - 2.87 (m, 2H), 1.82 - 1.71 (m, 2H), 0.85 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).

[0429] Intermediate G. [(Tricyclo[6.2.0.0^{3,6}]deca-1,3(6),7-trien-2-yl) carbamoyl]amino]-sulfonyl chloride.



[0430] General procedure D was followed using tricyclo[6.2.0.0^{3,6}]deca-1(8),2,6-trien-2-amine to give the title compound as a white solid (Y = 63 %) as a white solid, which was used immediately. LC-MS (ESI): m/z : $[\text{M}+\text{MeOH}-\text{Cl}]^+ = 283.2$.

Example 1 (compound 1). Sodium [(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl][(1-methyl-1H-pyrazol-4-yl)][(oxolan-2-yl)methyl]sulfamoyl]azanide

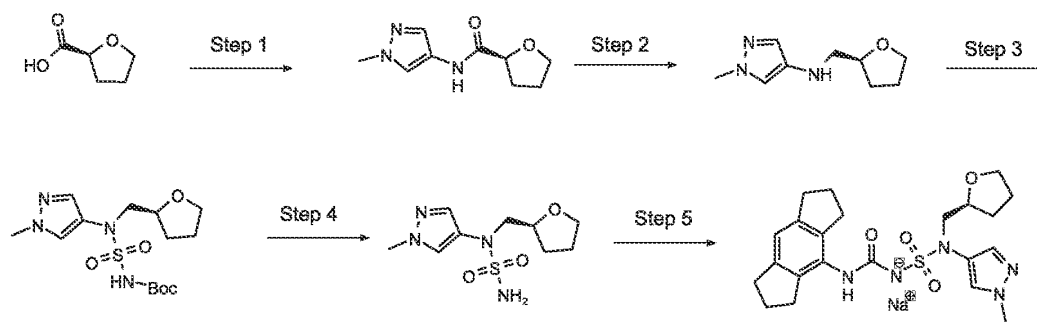


[0431] **Step 1. N-(1-Methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide.** General procedure A was followed using oxolane-2-carboxylic acid and 1-methyl-1H-pyrazol-4-amine. FCC (SiO_2 , 50 – 100 % EtOAc in pet. ether) gave the title compound as a yellow oil. ^1H NMR (400 MHz, MeOD) δ 7.90 (s, 1H), 7.58 (s, 1H), 4.42 - 4.38 (m, 1H), 4.13 - 4.02 (m, 1H), 3.93 - 3.87 (m, 1H), 3.85 (s, 3H), 2.36 - 2.27 (m, 1H), 2.05 - 1.89 (m, 3H).

[0432] **Step 2. 1-Methyl-N-[(oxolan-2-yl)methyl]-1H-pyrazol-4-amine.** General procedure B was followed using N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide to give the title compound as a yellow gum (Y = 79 %). ¹H NMR (400 MHz, MeOD) δ 7.16 (s, 1H), 7.12 (s, 1H), 4.09 - 4.05 (m, 1H), 3.89 - 3.84 (m, 1H), 3.77 (s, 3H), 3.73 - 3.71 (m, 1H), 3.03 - 2.91 (m, 2H), 2.05 - 2.00 (m, 1H), 1.95 - 1.89 (m, 2H), 1.68 - 1.59 (m, 1H).

[0433] **Step 3. Sodium [(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl][(1-methyl-1H-pyrazol-4-yl)((oxolan-2-yl)methyl)sulfamoyl]azanide.** General procedure C was followed using 1-methyl-N-(tetrahydrofuran-2-ylmethyl) pyrazol-4-amine, {[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino} sulfonyl chloride (intermediate A) and NaH. Prep-HPLC (column: Agela DuraShell C18, 10 μm, 250 x 50 mm; mobile phase: [water (10 mM NH₄HCO₃) - ACN]; B: 2 - 35 %, 23 min) gave the title compound as a white solid. Y = 5 %. ¹H NMR (400 MHz, MeOD) δ 7.76 (s, 1H), 7.54 (s, 1H), 6.99 (s, 1H), 4.00 - 3.80 (m, 1H), 3.78 (s, 3H), 3.75 - 3.68 (m, 4H), 2.88 (t, J = 7 Hz, 4H), 2.77 (t, J = 7 Hz, 4H), 2.11 - 2.04 (m, 4H), 2.95 - 1.94 (m, 3H), 1.65 - 1.64 (m, 1H). LCMS (ESI): m/z: [M+H]⁺ = 460.2.

Example 2 (Compound 1A). Sodium [(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl][(1-methyl-1H-pyrazol-4-yl)((2S)-oxolan-2-yl)methyl)sulfamoyl]azanide



[0434] **Step 1. (2S)-N-(1-Methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide.** General procedure A was followed using (2S)-tetrahydrofuran-2-carboxylic acid and 1-methylpyrazol-4-amine. Prep-HPLC (column: Phenomenex Luna C18, 10 μm, 250 x 100 mm; mobile phase: [water (0.1 % TFA) - ACN]; B: 0 - 14 %, 40 min) to give the title compound as a brown gum. Y = 74 %. ¹H NMR (400 MHz, MeOD) δ 7.92 (s, 1H), 7.60 (s, 1H), 4.42 - 4.39 (m, 1H), 4.11 - 4.04 (m, 1H), 3.93 - 3.89 (m, 1H), 3.86 (s, 3H), 2.34 - 2.29 (m, 1H), 2.07 - 2.02 (m, 1H), 1.98 - 1.88 (m, 2H).

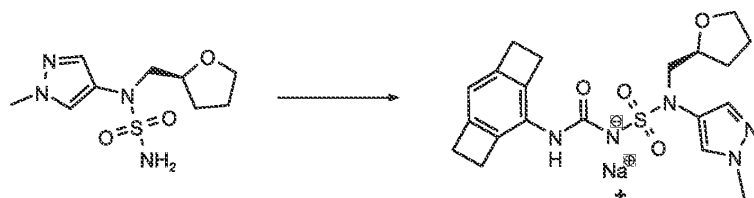
[0435] **Step 2. 1-Methyl-N-([(2S)-oxolan-2-yl]methyl)-1H-pyrazol-4-amine.** General procedure B was followed using (2S)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide to give the title compound, used without further purification. Y = 55 %. ¹H NMR (400 MHz, MeOD) δ 7.16 (s, 1H), 7.12 (s, 1H), 4.07 - 4.04 (m, 1H), 3.89 - 3.86 (m, 1H), 3.77 - 3.73 (m, 4H), 3.00 - 2.94 (m, 2H), 2.04 - 1.99 (m, 1H), 1.95 - 1.89 (m, 2H), 1.66 - 1.61 (m, 1H).

[0436] **Step 3. Tert-butyl N-[(1-methyl-1H-pyrazol-4-yl)([(2S)-oxolan-2-yl]methyl))-sulfamoyl]carbamate.** General procedure E was followed using 1-methyl-N-[(2S)-tetrahydrofuran-2-yl]methyl]pyrazol-4-amine. FCC (SiO₂, 0 - 50 % EtOAc in Pet. Ether) gave the title compound as a colourless gum. Y = 76 %. ¹H NMR (400 MHz, MeOD) δ 7.69 (s, 1H), 7.46 (s, 1H), 4.02 - 3.96 (m, 1H), 3.86 (s, 3H), 3.79 - 3.71 (m, 4H), 1.98 - 1.88 (m, 3H), 1.73 - 1.59 (m, 1H), 1.49 (s, 9H).

[0437] **Step 4. N-(1-Methyl-1H-pyrazol-4-yl)-N-([(2S)-oxolan-2-yl]methyl)amino-sulfonamide.** General procedure F was followed using N-[(1-methylpyrazol-4-yl)-[(2S)-tetrahydrofuran-2-yl]methyl] sulfamoyl]carbamate to give the title compound as a colourless gum. Y = 85 %. ¹H NMR (400 MHz, MeOD) δ 7.71 (s, 1H), 7.52 (s, 1H), 4.12 - 3.97 (m, 1H), 3.86 - 3.75 (m, 4H), 3.78 - 3.71 (m, 1H), 3.65 - 3.57 (m, 1H), 3.45 - 3.38 (m, 1H), 2.02 - 1.80 (m, 3H), 1.70 - 1.60 (m, 1H).

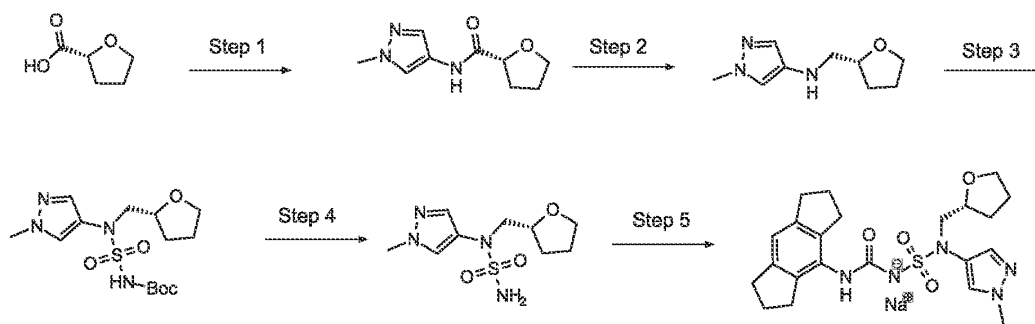
[0438] **Step 5. Sodium [(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl][(1-methyl-1H-pyrazol-4-yl)([(2S)-oxolan-2-yl]methyl))sulfamoyl]azanide.** To a solution of 1-methyl-4-[sulfamoyl-[(2S)-tetrahydrofuran-2-yl]methyl]amino]pyrazole (1.2 g, 4.61 mmol) and 4-isocyanato-1,2,3,5,6,7-hexahydro-s-indacene (919 mg, 4.61 mmol) in THF (20 mL) was added NaOH (184 mg, 4.61 mmol) at 0° C. The mixture was stirred at 0° C for 12 h. The reaction mixture was filtered to afford a clear filtrate. MTBE (40 mL) was added and the resulting solid collected by filtration and freeze dried from water to give the title compound as a white solid. Y = 66 %. ¹H NMR (400 MHz, MeOD) δ 7.64 (s, 1H), 7.52 (s, 1H), 6.87 (s, 1H), 3.99 - 3.93 (m, 1H), 3.84 - 3.75 (m, 4H), 3.69 - 3.58 (m, 3H), 2.84 (t, J = 7 Hz, 4H), 2.76 (t, J = 7 Hz, 4H), 2.08 - 1.99 (m, 4H), 1.97 - 1.70 (m, 3H), 1.78 - 1.68 (m, 1H). LCMS (ESI): m/z: [M+H]⁺ = 460.2.

Example 3 (Compound 3A). Sodium [(1-methyl-1H-pyrazol-4-yl)(({(2S)-oxolan-2-yl)methyl}))sulfamoyl]-((tricyclo[6.2.0.0^{3,6}]deca-1,3(6),7-trien-2-yl)carbamoyl)azanide



[0439] To a solution of 1-methyl-4-[sulfamoyl-[(2S)-tetrahydrofuran-2-yl]methyl]amino]-pyrazole (85 mg, 286 μ mol) in THF (1 mL) at 0° C was added NaOH (45.8 mg, 1.15 mmol). After 15 minutes, 10-isocyanatotricyclodeca- (6),7(9),8(10)-triene (Intermediate D) (49.0 mg, 286 μ mol) was added and the RM stirred at 0° C for 1 h. The reaction was concentrated *in vacuo*. Prep-HPLC (column: Waters Xbridge BEH C18, 10 μ m, 100 x 30 mm; mobile phase: [water (10 mM NH₄HCO₃) - ACN]; B: 12 – 42 %, 8 min) gave the title compound as a white solid. Y = 24 %. ¹H NMR (400 MHz, MeOD) δ 7.66 (s, 1H), 7.50 (s, 1H), 6.47 (s, 1H), 4.05 - 3.93 (m, 1H), 3.85 - 3.75 (m, 4H), 3.74 - 3.65 (m, 3H), 3.10 (s, 4H), 2.99 (s, 4H), 1.96 - 1.86 (m, 3H), 1.73 - 1.71 (m, 1H). LCMS (ESI): m/z: [M+H]⁺ = 432.2.

Example 4 (Compound 1B). Sodium [(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl][(1-methyl-1H-pyrazol-4-yl)(({(2R)-oxolan-2-yl)methyl}))sulfamoyl]azanide



[0440] **Step 1. (2R)-N-(1-Methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide.** To a solution of (2R)-oxolane-2-carboxylic acid (150 g, 1.29 mol) and 1-methyl-1H-pyrazol-4-aminium chloride (190 g, 1.42 mol) in EtOAc (900 mL) was added dropwise DIPEA (501 g, 3.88 mol) and T₃P (50 % solution in EtOAc, 1.29 mol) at 0° C. The RM was stirred at 15 - 20° C for 12 h. The RM was filtered and the filtrate concentrated *in vacuo*. FCC (SiO₂, 20 – 50 % EtOAc in Pet. Ether) gave

the title compound as a yellow solid (Y = 78 %). ¹H NMR (400 MHz, MeOD) δ 7.91 (s, 1H), 7.57 (s, 1H), 4.38 - 4.42 (m, 1H), 4.03 - 4.07 (m, 1H), 3.88 - 3.92 (m, 1H), 3.84 (s, 3H), 2.29 - 2.34 (m, 1H), 1.89 - 2.05 (m, 3H).

[0441] **Step 2. 1-Methyl-N-([(2R)-oxolan-2-yl]methyl)-1H-pyrazol-4-amine.** To a solution of (2R)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide (75.0 g, 384 mmol) in THF (450 mL) was added LiAlH₄ (72.9 g, 1.92 mol) at 0° C under N₂. The mixture was stirred at 80° C for 1 h under N₂. The RM was cooled to 0° C, water (75 mL) and NaOH (75 mL 15 % wt in water) and water (225 mL) was added dropwise to the solution at 0 - 5° C in sequence. The suspension was filtered and the filter cake washed (THF, 4 x 150 mL). The filtrate was concentrated *in vacuo* to give the title compound as an oil (Y = 77 %). ¹H NMR (400 MHz, MeOD) δ 7.16 (s, 1H), 7.12 (s, 1H), 4.06 - 4.04 (m, 1H), 3.88 - 3.86 (m, 1H), 3.78 - 3.74 (m, 4H), 3.02 - 2.91 (m, 2H), 2.04 - 1.89 (m, 3H), 1.66 - 1.59 (m, 1H).

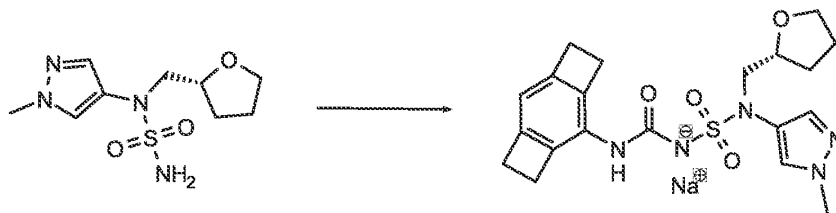
[0442] **Step 3. Tert-butyl N-[(1-methyl-1H-pyrazol-4-yl)([(2R)-oxolan-2-yl]methyl)-sulfamoyl]carbamate.** To a solution of 1-methyl-N-[(2R)-tetrahydrofuran-2-yl]methylpyrazol-4-amine (115 g, 635 mmol) in THF (690 mL) at 0° C was added DIPEA (221 mL, 1.27 mol) and tert-butyl N-(chlorosulfonyl)carbamate (205 g, 952 mmol) in THF (880 mL) and the RM stirred at 0° C for 1 hr. The RM was diluted (water, 1.5 L), extracted (EtOAc, 2 x 1L). The combined organic phase was washed with water (1.0 L) and brine (1.0 L), dried over Na₂SO₄ and concentrated *in vacuo*. FCC (SiO₂, 10 - 30 % EtOAc in Pet. Ether) gave the crude product. Trituration with MTBE (600 mL) at 20° C for 2 h followed by filtration and drying *in vacuo* at 45° C for 4 h gave the title compound as a white solid. Y = 76 %. ¹H NMR (400, MHz MeOD) δ 7.70 (s, 1H), 7.47 (s, 1H), 4.00 - 3.97 (m, 1H), 3.86 - 3.72 (m, 7H), 1.96 - 1.86 (m, 3H), 1.67 - 1.66 (m, 1H), 1.49 (s, 9H).

[0443] **Step 4. N-(1-Methyl-1H-pyrazol-4-yl)-N-([(2R)-oxolan-2-yl]methyl)amino-sulfonamide.** N-[(1-Methylpyrazol-4-yl)-[(2R)-tetrahydrofuran-2-yl]methyl] sulfamoyl]-carbamate (205 g, 569 mmol) was dissolved in 4 M HCl in EtOAc (1200 mL) and stirred at 15 - 20° C for 12 h. The RM was concentrated *in vacuo* and the residue was triturated with EtOAc (500 mL) at 20° C for 30 min. The solid was collected by filtration. The solid was dissolved into water (600 mL) and the pH adjusted to 8 with saturated Na₂CO₃ aqueous solution. The solution was extracted (EtOAc, 2 x 500 mL). The combined organic phase was washed with water (500 mL) and brine (500 mL), dried over Na₂SO₄ and concentrated *in vacuo* to give the title compound

as a white solid. Y = 80 %. ^1H NMR (400 MHz, MeOD) δ 7.71 (s, 1H), 7.52 (s, 1H), 4.07 - 4.02 (m, 1H), 3.86 - 3.81 (m, 4H), 3.76 - 3.71 (m, 1H), 3.64 - 3.59 (m, 1H), 3.44 - 3.40 (m, 1H), 2.02 - 1.82 (m, 3H), 1.69 - 1.59 (m, 1H).

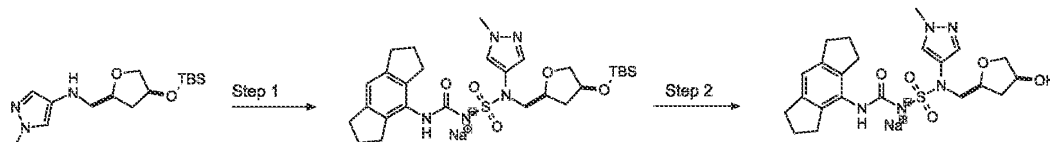
[0444] **Step 5. Sodium [(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl][(1-methyl-1H-pyrazol-4-yl)(([(2R)-oxolan-2-yl]methyl))sulfamoyl]azanide.** To a solution of 1-methyl-4-[sulfamoyl-[(2R)-tetrahydrofuran-2-yl]methyl]amino]pyrazole (59.5 g, 229 mmol) and 4-isocyanato-1,2,3,5,6,7-hexahydro-s-indacene (45.5 g, 229 mmol) in THF (900 mL) at 0° C was added NaOH (9.14 g, 229 mmol) and the RM stirred at 15° C for 12 h. The RM was filtered. MTBE (5.4 L) was added dropwise to the filtrate and the solid was collected by filtration, washed with MTBE (2 x 500 mL), dried *in vacuo* and freeze-dried from water (1 L) to give the title compound as an off-white solid. Y = 73 %. ^1H NMR (400 MHz, MeOD) δ 7.64 (s, 1H), 7.52 (s, 1H), 6.87 (s, 1H), 4.00 - 3.93 (m, 1H), 3.86 - 3.78 (m, 4H), 3.70 - 3.65 (m, 2H), 3.57 - 3.52 (m, 1H), 2.84 (t, J = 7.2 Hz, 4H), 2.77 (t, J = 7.2 Hz, 4H), 2.06 - 1.99 (m, 4H), 1.98 - 1.80 (m, 3H), 1.73 - 1.65 (m, 1H). LCMS (ESI): m/z : $[\text{M}+\text{H}]^+ = 460.2$.

Example 5 (Compound 3B). Sodium [(1-methyl-1H-pyrazol-4-yl)(([(2R)-oxolan-2-yl]methyl))sulfamoyl]-((tricyclo[6.2.0.0^{3,6}]deca-1,3(6),7-trien-2-yl)carbamoyl)azanide



[0445] General procedure G was followed using 1-methyl-4-[sulfamoyl-[(2R)-tetrahydrofuran-2-yl]methyl]amino]pyrazole and 10-isocyanatotricyclodeca-(6,7(9),8(10))-triene. Prep-HPLC (column: Waters Xbridge BEH C18, 10 μm , 100 x 30 mm; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B: 12 - 42 %, 8 min) gave the title compound as a white solid. Y = 14 %. ^1H NMR (400 MHz, MeOD) δ 7.71 (s, 1H), 7.51 (s, 1H), 6.52 (s, 1H), 4.01 - 3.82 (m, 1H), 3.80 - 3.74 (m, 5H), 3.73 - 3.71 (m, 2H), 3.12 - 3.10 (m, 4H), 3.03 - 3.01 (m, 4H), 1.97 - 1.88 (m, 3H), 1.72 - 1.69 (m, 1H). LCMS (ESI): m/z : $[\text{M}+\text{H}]^+ = 432.1$.

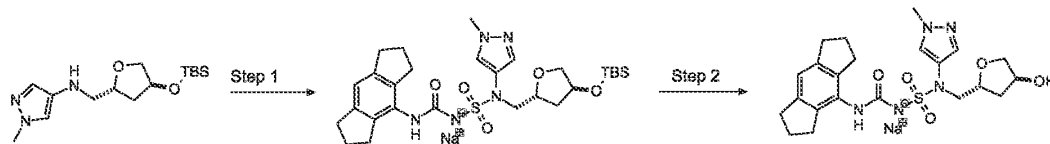
Example 6 (Compound 2A). Sodium ((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)(N-((cis-4-hydroxy-tetrahydrofuran-2-yl)methyl)-N-(1-methyl-1H-pyrazol-4-yl)sulfamoyl)amide.



[0446] **Step 1. 1-[[[(2S,4S)-4-[tert-butyl (dimethyl)silyl]oxytetrahydrofuran-2-yl]methyl-(1-methylpyrazol-4-yl)sulfamoyl]-3-(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)urea, sodium salt.** To a solution of syn-N-[[[(2S,4S)-4-[tert-butyl(dimethyl)silyl]oxytetrahydrofuran-2-yl]methyl]-1-methyl-pyrazol-4-amine (60 mg, 192.62 μ mol) in THF (1 mL) was added NaH (60 % in mineral oil, 46.2 mg, 1.16 mmol) at 0° C for 15 min, followed by N-(1,2,3,5,6,7-hexahydro-s-indacen-4-ylcarbamoyl)sulfamoyl chloride (1.38 mL, 0.14 M in isopropyl ether, 193 μ mol). The RM was stirred at 0° C for 30 min and concentrated *in vacuo* to give the title compound as a white solid. LCMS (ESI): m/z: $[M+H]^+$ = 590.3.

[0447] **Step 2. 1-(1,2,3,5,6,7-Hexahydro-s-indacen-4-yl)-3-[[[(2S,4S)-4-hydroxy-tetrahydrofuran-2-yl]methyl-(1-methylpyrazol-4-yl)sulfamoyl]urea.** To a solution of 1-[[[(2S,4S)-4-[tert-butyl(dimethyl)silyl]oxytetrahydrofuran-2-yl]methyl-(1-methylpyrazol-4-yl)sulfamoyl]-3-(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)urea (50 mg, 81.6 μ mol) in THF (1 mL) at 25° C was added pyridine hydrofluoride (0.2 mL, 2.22 mmol). The RM was stirred at 0° C for 30 min and treated with NaH (60 % in mineral oil, 444 mg, 11.1 mmol). The RM was stirred at 0° C for 10 min and concentrated *in vacuo*. Prep-HPLC (column: Waters Xbridge BEH C18, 10 μ m, 100 x 30 mm; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B: 5 – 35 %, 8 min) gave the title compound as a white solid. Y = 4 %. 1H NMR (400 MHz, MeOD) δ 7.75 (s, 1H), 7.54 (s, 1H), 6.97 (s, 1H), 4.39 - 4.36 (m, 1H), 4.07 - 4.04 (m, 1H), 4.00 - 3.95 (m, 1H), 3.87 (s, 3H), 3.83 - 3.82 (m, 1H), 3.69 - 3.68 (m, 2H), 2.87 (t, J = 8 Hz, 4H), 2.76 (t, J = 7 Hz, 4H), 2.27 - 2.22 (m, 1H), 2.11 - 2.03 (m, 4H), 1.68 - 1.60 (m, 1H). LCMS (ESI): m/z: $[M+H]^+$ = 476.2.

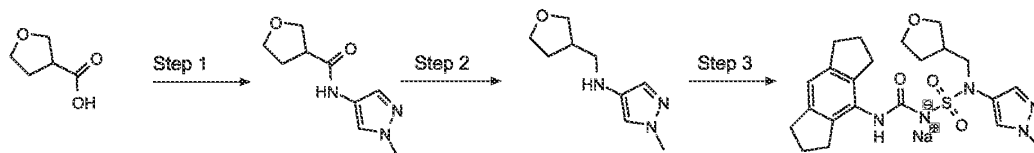
Example 7 (Compound 2B). 1-(1,2,3,5,6,7-Hexahydro-s-indacen-4-yl)-3-[[[(2R,4S)-4-hydroxytetrahydro-furan-2-yl]methyl-(1-methylpyrazol-4-yl)sulfamoyl]urea, sodium salt.



[0448] **Step 1.** 1-[[[(2R,4S)-4-[Tert-butyl (dimethyl)silyl]oxytetrahydrofuran-2-yl]methyl-(1-methylpyrazol-4-yl)sulfamoyl]-3-(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)urea, sodium salt. To a solution of anti-N-[[[(2R,4S)-4-[tert-butyl(dimethyl)silyl]oxytetrahydrofuran-2-yl]methyl]-1-methyl-pyrazol-4-amine (60 mg, 192.62 μ mol) in THF (1 mL) at 0° C was added NaH (60 % in mineral oil, 46.2 mg, 1.16 mmol) and the RM stirred for 15 min. N-(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)sulfamoyl chloride (0.14 M, 1.38 mL in isopropyl ether, 193 μ mol) was added at 0° C and the RM stirred for 30 min. The RM was concentrated *in vacuo* to give the title compound as a white solid, used without further purification. LCMS (ESI): m/z: [M+H]⁺ = 590.3.

[0449] **Step 2.** 1-(1,2,3,5,6,7-Hexahydro-s-indacen-4-yl)-3-[[[(2R,4S)-4-hydroxytetrahydrofuran-2-yl]methyl-(1-methylpyrazol-4-yl)sulfamoyl]urea. To a solution of 1-[[[(2R,4S)-4-[tert-butyl(dimethyl)silyl]oxytetrahydrofuran-2-yl]methyl-(1-methylpyrazol-4-yl)sulfamoyl]-3-(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)urea (60 mg, 97.9 μ mol) in THF (1.5 mL) at 25° C was added pyridine hydrofluoride (0.3 mL, 3.33 mmol). After stirring at 25° C for 30 min, the reaction was cooled to 0° C and treated with NaH (133 mg, 60 % in mineral oil, 3.33 mmol). The RM was stirred at 0° C for 10 min. The reaction mixture was concentrated *in vacuo*. Prep-HPLC (column: Waters Xbridge BEH C18, 10 μ m, 100 x 30 mm; mobile phase: [water (10 mM NH₄HCO₃) - ACN]; B: 5 – 35 %, 8 min) gave the title compound as a white solid. Y = 4 %. ¹H NMR (400 MHz, MeOD) δ 7.75 (s, 1H), 7.54 (s, 1H), 6.98 (s, 1H), 4.42 - 4.38 (m, 1H), 4.26 - 4.21 (m, 1H), 3.89 - 3.85 (m, 5H), 3.77 - 3.73 (m, 1H), 3.61 - 3.59 (m, 1H), 2.87 (t, *J* = 7 Hz, 4H), 2.76 (t, *J* = 7 Hz, 4H), 2.11 - 2.04 (m, 4H), 1.98 - 1.90 (m, 1H), 1.85 - 1.79 (m, 1H). LCMS (ESI): m/z: [M+H]⁺ = 476.2.

Example 8 (Compound 4). Sodium [(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl][(1-methyl-1H-pyrazol-4-yl)((oxolan-2-yl)methyl)sulfamoyl]azanide

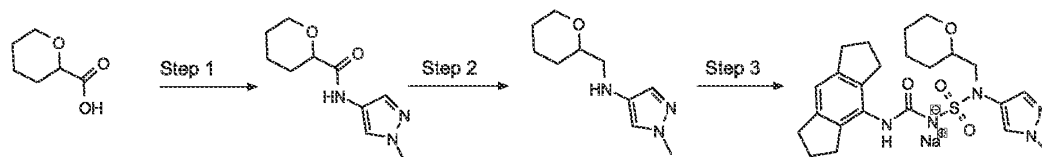


[0450] **Step 1. N-(1-Methylpyrazol-4-yl) tetrahydrofuran-3-carboxamide.** General procedure A was followed using tetrahydrofuran-3-carboxylic acid and 1-methylpyrazol-4-amine. FCC (SiO₂, 5 - 50 % MeOH in EtOAc) gave the title compound as a white solid (Y = 59 %). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.00 (s, 1H), 7.85 (s, 1H), 7.38 (s, 1H), 3.90 (t, *J* = 8 Hz, 1H), 3.77 (s, 3H), 3.76 - 3.64 (m, 3H), 3.09 - 3.01 (m, 1H), 2.07 - 1.99 (m, 2H).

[0451] **Step 2. N-(1-Methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide.** General procedure B was followed using N-(1-methylpyrazol-4-yl)tetrahydrofuran-3-carboxamide to give the title compound as a colourless oil (Y = 79 %), which was used into the next step directly without further purification.

[0452] **Step 3. Sodium [(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl][(1-methyl-1H-pyrazol-4-yl)((oxolan-2-yl)methyl)sulfamoyl]azanide.** General procedure C was followed using 1-methyl-N-(tetrahydrofuran-3-ylmethyl)pyrazol-4-amine, {[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino} sulfonyl chloride (intermediate A) and NaH. Prep-HPLC (column: Waters Xbridge BEH C18, 5 μm, 100 x 25 mm; mobile phase: [water (10 mM NH₄HCO₃) - ACN]; B: 10 - 40 %, 10 min) gave the title compound as a white solid. Y = 16 %. ¹H NMR (400 MHz, DMSO-*d*₆) 7.80 (s, 1H), 7.76 (s, 1H), 7.40 (s, 1H), 6.95 (s, 1H), 3.81 (s, 3H), 3.73 - 3.65 (m, 1H), 3.65 - 3.52 (m, 4H), 3.41 - 4.32 (m, 1H), 2.81 (t, *J* = 7 Hz, 4H), 2.68 (t, *J* = 7 Hz, 4H), 2.30 - 2.17 (m, 1H), 2.03 - 1.93 (m, 4H), 1.90 - 1.79 (m, 1H), 1.58 - 1.46 (m, 1H). LCMS (ESI): *m/z*: [M+H]⁺ = 460.1.

Example 9 (Compound 6). Sodium [(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl][(1-methyl-1H-pyrazol-4-yl)[(oxan-2-yl)methyl]sulfamoyl]azanide



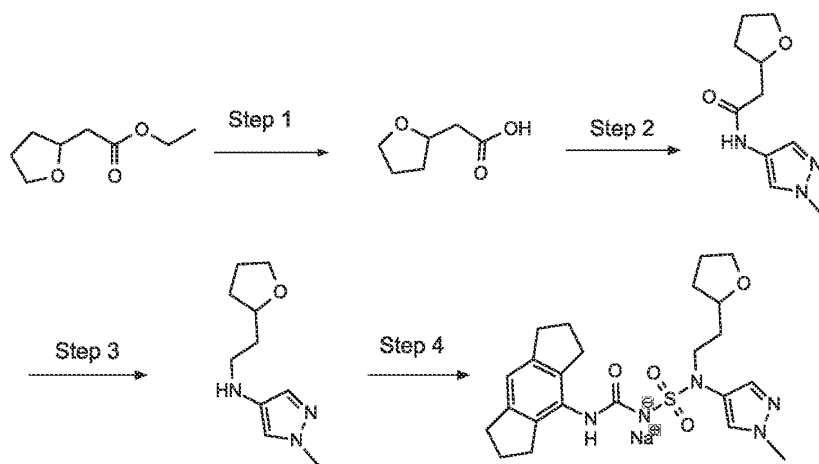
[0453] **Step 1. N-(1-Methyl-1H-pyrazol-4-yl)oxane-2-carboxamide.** General procedure A was followed using oxane-2-carboxylic acid and 1-methylpyrazol-4-amine. FCC (SiO₂, 10 - 100 % EtOAc in pet. ether) gave the title compound as a yellow solid (Y = 68 %). ¹H NMR (400 MHz, MeOD) δ 7.89 (s, 1H), 7.56 (s, 1H), 4.13 - 4.09 (m, 1H), 3.92 - 3.89 (m, 1H), 3.84 (s, 3H), 3.59 - 3.53 (m, 1H), 2.09 - 1.98 (m, 1H), 1.94 - 1.87 (m, 1H), 1.70 - 1.57 (m, 3H), 1.51 - 1.40 (m, 1H).

[0454] **Step 2. 1-Methyl-N-[(oxan-2-yl)methyl]-1H-pyrazol-4-amine.** General procedure B was followed using N-(1-methyl-1H-pyrazol-4-yl)oxane-2-carboxamide to give the title compound as a colourless oil (Y = 82 %), which was used into the next step directly without further purification. ¹H NMR (400 MHz, MeOD) δ 7.15 (s, 1H), 7.12 (s, 1H), 3.99 - 3.94 (m, 1H), 3.77 (s, 3H), 3.54 - 3.40 (m, 2H), 2.95 - 2.86 (m, 2H), 1.92 - 1.82 (m, 1H), 1.64 - 1.49 (m, 4H), 1.40 - 1.30 (m, 1H).

[0455] **Step 3. Sodium [(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl][(1-methyl-1H-pyrazol-4-yl)[(oxan-2-yl)methyl]sulfamoyl]azanide.** General procedure C was followed using 1-methyl-N-[(oxan-2-yl)methyl]-1H-pyrazol-4-amine, {[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino)sulfonyl chloride (intermediate A) and NaH. Prep-HPLC (column: Phenomenex Gemini-NX C18, 3 μm, 75 × 30 mm; mobile phase: [water (10 mM NH₄HCO₃) - ACN]; B: 20 - 40 %, 8 min) gave the title compound as a white solid. Y = 8 %. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.77 (s, 1H), 7.75 (s, 1H), 7.37 (s, 1H), 6.95 (s, 1H), 3.81 - 3.78 (m, 4H), 3.64 - 3.53 (m, 2H), 3.26 - 3.21 (m, 2H), 2.81 (t, *J* = 7 Hz, 4H), 2.67 (t, *J* = 7 Hz, 4H), 2.03 - 1.93 (m, 4H), 1.76 - 1.68 (m, 1H), 1.62 - 1.52 (m, 1H), 1.47 - 1.31 (m, 3H), 1.14 - 1.05 (m, 1H).

LCMS (ESI): *m/z*: [M+H]⁺ = 474.2.

Example 10 (Compound 5). Sodium [(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl][(1-methyl-1H-pyrazol-4-yl)[2-(oxolan-2-yl) ethyl]sulfamoyl]azanide



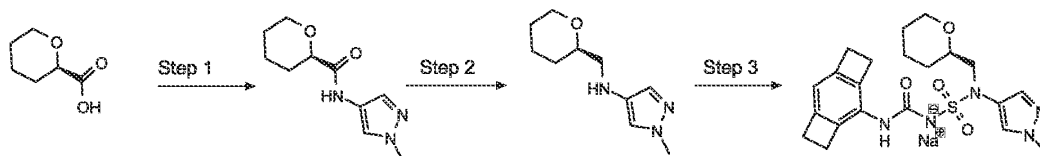
[0456] **Step 1. 2-(Oxolan-2-yl)acetic acid.** To a solution of ethyl 2-(oxolan-2-yl) acetate (500 mg, 3.16 mmol) in H₂O (2.5 mL) and MeOH (2.5 mL) at 0° C was added LiOH·H₂O (133 mg, 3.16 mmol) and the RM stirred at 0° C for 30 min. The RM was treated dropwise with 1 M HCl until the pH reached 5. The solution was extracted (EtOAc, 5 x 10 mL). The combined organic layers were concentrated *in vacuo* to give the title compound, which was used without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.20 – 12.00 (br. s, 1H), 4.10 - 4.03 (m, 1H), 3.81 - 3.68 (m, 1H), 3.64 - 3.50 (m, 1H), 2.38 (d, *J* = 6 Hz, 2H), 2.06 - 1.92 (m, 1H), 1.94 - 1.78 (m, 2H), 1.53 - 1.39 (m, 1H).

[0457] **Step 2. N-(1-Methyl-1H-pyrazol-4-yl)-2-(oxolan-2-yl)acetamide.** General procedure A was followed using 2-(oxolan-2-yl)acetic acid and 1-methylpyrazol-4-amine. FCC (SiO₂, 0 - 100 % EtOAc in pet. ether) gave the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.87 (s, 1H), 7.83 (s, 1H), 7.36 (s, 1H), 4.14 - 4.11 (m, 1H), 3.84 - 3.70 (m, 4H), 3.60 - 3.50 (m, 1H), 2.47 - 2.30 (m, 2H), 2.01 - 1.96 (m, 1H), 1.88 - 1.74 (m, 2H), 1.57 - 1.43 (m, 1H).

[0458] **Step 3. 1-Methyl-N-[2-(oxolan-2-yl)ethyl]-1H-pyrazol-4-amine.** General procedure B was followed using N-(1-Methyl-1H-pyrazol-4-yl)-2-(oxolan-2-yl)acetamide to give the title compound as a gum, which was used into the next step directly without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.01 (s, 1H), 6.90 (s, 1H), 4.29 - 4.16 (m, 1H), 3.86 - 3.70 (m, 2H), 3.67 (s, 3H), 3.62 - 3.52 (m, 1H), 2.93 - 2.76 (m, 2H), 2.00 - 1.87 (m, 1H), 1.85 - 1.73 (m, 2H), 1.70 - 1.57 (m, 2H), 1.45 - 1.36 (m, 1H).

[0459] **Step 4. Sodium [(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl][(1-methyl-1H-pyrazol-4-yl)[2-(oxolan-2-yl)ethyl]sulfamoyl]azanide.** General procedure C was followed using 1-methyl-N-[2-(oxolan-2-yl)ethyl]-1H-pyrazol-4-amine, {[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}sulfonyl chloride (intermediate A) and NaH. Prep-HPLC (column: Waters Xbridge Prep OBD C18, 10 μ m, 40 x 10 mm; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B: 20 – 40 %, 8 min) gave the title compound as a white solid. Y = 10 %. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.30 – 10.10 (br. s, 1H), 7.79 (s, 2H), 7.38 (s, 1H), 6.96 (s, 1H), 3.82 (s, 3H), 3.76 – 3.60 (m, 4H), 3.57 – 3.49 (m, 1H), 2.82 (t, J = 7 Hz, 4H), 2.68 (t, J = 7 Hz, 4H), 2.04 – 1.94 (m, 4H), 1.98 – 1.86 (m, 1H), 1.81 – 1.70 (m, 2H), 1.63 – 1.52 (m, 2H), 1.40 – 1.29 (m, 1H). LCMS (ESI): m/z : $[\text{M}+\text{H}]^+ = 474.1$.

Example 11 (Compound 7B). Sodium [(1-methyl-1H-pyrazol-4-yl)((2R)-oxan-2-yl)methyl]sulfamoyl-((tricyclo[6.2.0.0.3,6]deca-1,3(6),7-trien-2-yl)carbamoyl)azanide



[0460] **Step 1. (2R)-N-(1-Methyl-1H-pyrazol-4-yl)oxane-2-carboxamide.** General procedure A was followed using (2R)-oxane-2-carboxylic acid and 1-methylpyrazol-4-amine. FCC (SiO_2 , 5 – 50 % MeOH in EtOAc) gave the title compound as a white solid. Y = 83 %. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.75 – 9.65 (br. s, 1H), 7.89 (s, 1H), 7.51 (s, 1H), 4.04 – 3.99 (m, 1H), 3.88 – 3.84 (m, 1H), 3.76 (s, 3H), 3.53 – 3.44 (m, 1H), 1.94 – 1.78 (m, 2H), 1.57 – 1.47 (m, 3H), 1.41 – 1.29 (m, 1H).

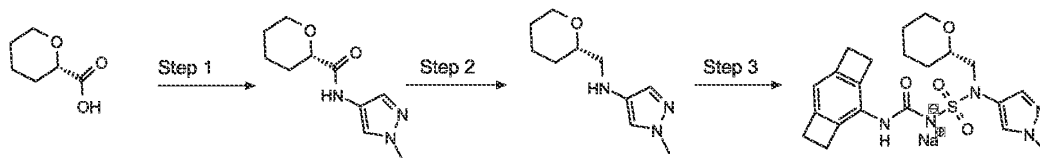
[0461] **Step 2. 1-Methyl-N-((2R)-oxan-2-yl)methyl-1H-pyrazol-4-amine.** General procedure B was followed using (2R)-N-(1-methyl-1H-pyrazol-4-yl)oxane-2-carboxamide to give the title compound as a colourless oil (Y = 89 %), which was used into the next step without further purification. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.02 (s, 1H), 6.92 (s, 1H), 4.19 (t, J = 6 Hz, 1H), 3.92 – 3.83 (m, 1H), 3.66 (s, 3H), 3.40 – 3.36 (m, 1H), 3.31 – 3.25 (m, 1H), 2.84 – 2.77 (m, 2H), 1.82 – 1.73 (m, 1H), 1.61 (d, J = 13 Hz, 1H), 1.48 – 1.40 (m, 3H), 1.25 – 1.10 (m, 1H).

[0462] **Step 3. Sodium [(1-methyl-1H-pyrazol-4-yl)((2R)-oxan-2-yl)methyl]sulfamoyl-((tricyclo[6.2.0.0.3,6]deca-1,3(6),7-trien-2-yl)carbamoyl)azanide.** General procedure C was

followed using methyl-N-(((2R)-oxan-2-yl)methyl)-1H-pyrazol-4-amine, [({tricyclo[6.2.0.0^{3,6}]-deca-1,3(6),7-trien-2-yl} carbamoyl)amino]sulfonyl chloride

(Intermediate G) and NaH. Prep-HPLC (column: Waters Xbridge Prep OBD C18, 10 μ m, 150 x 40 mm; mobile phase: [water (10 mM NH₄HCO₃) - ACN]; B: 15 – 45 %, 8 min) gave the title compound as a white solid. Y = 12 %. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.19 (s, 1H), 7.75 (s, 1H), 7.36 (s, 1H), 6.57 (s, 1H), 3.86 - 3.81 (m, 1H), 3.79 (s, 3H), 3.69 - 3.55 (m, 2H), 3.28 - 3.22 (m, 2H), 3.06 (s, 4H), 2.96 (s, 4H), 1.82 - 1.67 (m, 1H), 1.59 (d, *J* = 13 Hz, 1H), 1.48 - 1.30 (m, 3H), 1.20 - 1.03 (m, 1H). LCMS (ESI): *m/z*: [M+H]⁺ = 446.1.

Example 12 (Compound 7A). Sodium [(1-methyl-1H-pyrazol-4-yl)((2S)-oxan-2-yl)methyl)sulfamoyl]-({tricyclo[6.2.0.0^{3,6}]-deca-1,3(6),7-trien-2-yl} carbamoyl)azanide



[0463] **Step 1. (2S)-N-(1-Methyl-1H-pyrazol-4-yl)oxane-2-carboxamide.** General procedure A was followed using (2S)-oxane-2-carboxylic acid and 1-methylpyrazol-4-amine. FCC (SiO₂, 5 – 50 % MeOH in EtOAc) gave the title compound as a white solid. Y = 69 %. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.67 (s, 1H), 7.88 (s, 1H), 7.51 (s, 1H), 4.04 - 3.99 (m, 1H), 3.88 - 3.84 (m, 1H), 3.76 (s, 3H), 3.52 - 3.44 (m, 1H), 1.93 - 1.77 (m, 2H), 1.58 - 1.50 (m, 3H), 1.42 - 1.32 (m, 1H).

[0464] **Step 2. 1-Methyl-N-(((2S)-oxan-2-yl)methyl)-1H-pyrazol-4-amine.** General procedure B was followed using (2S)-N-(1-methyl-1H-pyrazol-4-yl)oxane-2-carboxamide to give the title compound as an oil (Y = 65 %), which was used into the next step without further purification.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.02 (s, 1H), 6.92 (s, 1H), 4.25 – 4.20 (br. s, 1H), 3.88 - 3.84 (m, 1H), 3.66 (s, 3H), 3.40 - 3.34 (m, 1H), 3.30 - 3.25 (m, 1H), 2.80 (d, *J* = 6 Hz, 2H), 1.81 - 1.71 (m, 1H), 1.65 - 1.58 (m, 1H), 1.50 - 1.34 (m, 3H), 1.26 - 1.11 (m, 1H).

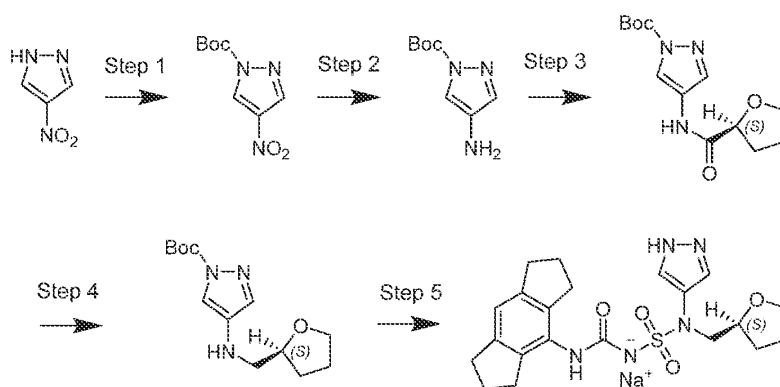
[0465] **Step 3. Sodium [(1-methyl-1H-pyrazol-4-yl)((2S)-oxan-2-yl)methyl)sulfamoyl]-({tricyclo[6.2.0.0^{3,6}]-deca-1,3(6),7-trien-2-yl} carbamoyl)azanide.** General procedure C was followed using methyl-N-(((2S)-oxan-2-yl)methyl)-1H-pyrazol-4-amine, [({tricyclo[6.2.0.0^{3,6}]-deca-1,3(6),7-trien-2-yl} carbamoyl)amino]sulfonyl chloride.

[0466] (Intermediate G) and NaH. Prep-HPLC (column: Waters Xbridge Prep OBD C18, 5 μ m, 100 x 25 mm; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B: 10 – 50 %, 10 min) gave the title compound as a white solid. Y = 21 %. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.94 (br. s, 1H), 8.16 (s, 1H), 7.73 (s, 1H), 7.35 (s, 1H), 6.56 (s, 1H), 3.84 - 3.79 (m, 4H), 3.71 - 3.54 (m, 2H), 3.27 - 3.20 (m, 2H), 3.05 (s, 4H), 2.96 (s, 4H), 1.78 - 1.66 (m, 1H), 1.59 (d, $J=13$ Hz, 1H), 1.41 - 1.36 (m, 3H), 1.16 - 1.07 (m, 1H).

[0467] ^1H NMR (400 MHz, $\text{DMSO}-d_6+\text{D}_2\text{O}$) δ 7.72 (s, 1H), 7.34 (s, 1H), 6.55 (s, 1H), 3.83 - 3.78 (m, 4H), 3.62 - 3.58 (m, 2H), 3.28 - 3.20 (m, 2H), 3.04 (s, 4H), 2.95 (s, 4H), 1.78 - 1.69 (m, 1H), 1.58 (d, $J=12$ Hz, 1H), 1.40 - 1.35 (m, 3H), 1.16 - 1.06 (m, 1H).

LCMS (ESI): m/z : $[\text{M}+\text{H}]^+ = 446.1$.

Example 13 (Compound 8A). 1-(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)-3-[1H-pyrazol-4-yl]-[(2S)-tetrahydrofuran-2-yl]methyl)sulfamoyl]urea



[0468] **Step 1. *tert*-Butyl 4-nitropyrzazole-1-carboxylate.** To a solution of 4-nitro-1H-pyrazole (15 g, 132.7 mmol) in THF (150 mL) was added di-*tert*-butyl decarbonate (33.5 mL, 145.9 mmol), DIPEA (23.1 mL, 132.7 mmol) and DMAP (1.62 g, 13.3 mmol) at 0° C. The mixture was stirred at 25° C for 2 h. Water (100 mL) was added and the resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , 20 – 25 % EtOAc in petroleum ether) to give the title compound as a white solid. Y = 50 %. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.30 (s, 1H), 8.53 (s, 1H), 1.60 (s, 9H).

[0469] **Step 2. *tert*-Butyl 4-aminopyrazole-1-carboxylate.** To a solution of *tert*-butyl 4-nitropyrzazole-1-carboxylate (5.0 g, 23.45 mmol) in MeOH (100 mL) was added 10 % Pd on carbon

(50 % wt. in water, 1.0 g) under N₂ atmosphere. The suspension was degassed and purged with H₂ three times. The mixture was stirred under H₂ (15 psi) at 25° C for 1 h. The reaction mixture was filtered through Celite and the filtrate concentrated under reduced pressure to give the title compound as a white solid. Y = 93 %. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.35 (s, 1H), 7.34 (s, 1H), 4.40 (s, 2H), 1.53 (s, 9H).

[0470] **Step 3. *Tert*-Butyl 4-[[[(2S)-tetrahydrofuran-2-carbonyl] amino] pyrazole-1-carboxylate.** To a solution of (2S)-tetrahydrofuran-2-carboxylic acid (951 mg, 8.19 mmol) in DMF (30 mL) was added *tert*-butyl 4-aminopyrazole-1-carboxylate (1.5 g, 8.19 mmol), DIPEA (5.70 mL, 32.75 mmol) and T₃P (50 % solution in EtOAc, 5.73 g, 9.01 mmol). The RM was stirred at 25° C for 2 h. Water (20 mL) was added and the product extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and the filtrate concentrated under reduced pressure. The residue was purified by silica gel chromatography (10 – 30 % EtOAc in petroleum ether) to give the title compound as a solid. Y = 91 %.

[0471] **Step 4. *tert*-Butyl 4-[[[(2S)-tetrahydrofuran-2-yl]methylamino]pyrazole-1-carboxylate.** To a solution of *tert*-butyl 4-[[[(2S)-tetrahydrofuran-2-carbonyl]amino]pyrazole-1-carboxylate (1.8 g, 6.40 mmol) in THF (100 mL) at 0° C was added 10 M borane dimethyl sulfide complex (2.56 ml, 25.6 mmol). The RM was stirred at 80° C for 3 h. The RM was cooled to 0° C and added dropwise to MeOH (50 mL). The mixture was concentrated under reduced pressure to give the title compound as a yellow gum, which was used without purification. LCMS (ESI): m/z: [M+H]⁺ = 268.2.

[0472] **Step 5. 1-(1,2,3,5,6,7-Hexahydro-s-indacen-4-yl)-3-[1H-pyrazol-4-yl-[[[(2S)-tetrahydrofuran-2-yl]methyl]sulfamoyl]urea.** General procedure C was followed using *tert*-butyl 4-[[[(2S)-tetrahydrofuran-2-yl]methylamino]pyrazole-1-carboxylate, {(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino} sulfonyl chloride (intermediate A) and NaH. Prep-HPLC (column: Phenomenex Titank C18 Bulk 250 x 70mm 10 μ m; mobile phase: [water (10 mM NH₄HCO₃) – ACN]; B: 15 – 45 %, 20 min) gave the 0.5 eq sodium salt of the title compound as a white solid. Y = 12 %. ¹H NMR (400 MHz, MeOD) δ 7.83 – 7.58 (m, 2H), 6.92 (s, 1H), 4.04 – 3.96 (m, 1H), 3.82 – 3.63 (m, 4H), 2.85 (t, *J* = 7 Hz, 4H), 2.76 (t, *J* = 7 Hz, 4H), 2.10 – 2.00 (m, 4H), 1.99 – 1.78 (m, 3H), 1.76 – 1.67 (m, 1H). LCMS (ESI): m/z: [M+H]⁺ = 446.2.

In Vitro Profiling of the Compounds of the Present Disclosure.

[0473] The biological activity of the compounds of the present disclosure was determined utilizing the assays described herein.

[0474] **PBMC IC₅₀ Determination Assay.** The compounds of the present disclosure were tested for their inhibitory activity against IL-1 β release upon NLRP3 activation in peripheral blood mononuclear cells (PBMC).

[0475] **Protocol A.** PBMC were isolated from buffy coats by density gradient centrifugation on Histopaque-1077 (Sigma, cat no. 10771). Isolated cells were seeded into the wells of a 96-well plate and incubated for 3 h with lipopolysaccharide (LPS). Following medium exchange, the compounds of the present disclosure were added (a single compound per well) and the cells were incubated for 30 min. Next, the cells were stimulated either with ATP (5 mM) or nigericin (10 μ M) for 1 h and the cell culture media from the wells were collected for further analysis. The release of IL-1 β into the media was determined by a quantitative detection of IL-1 β in the media using an IL-1 β enzyme-linked immunosorbent assay (ELISA) Ready-SET-Go!, eBioscience cat. No. 88-7261-88. Briefly, in a first step, high affinity binding plates (Corning, Costar 9018 or NUNC Maxisorp Cat No. 44-2404) were coated overnight at 4° C with specific capture antibody included in the kit (anti-human IL-1 β ref. 14-7018-68). Subsequently, plates were blocked with blocking buffer for 1 h at room temperature (rt) and after washing with a buffer (PBS with 0.05 % Tween-20) incubated with protein standard and culture media. After 2 h of incubation at rt, plates were washed and incubated with biotinylated detection antibody included in the kit (anti-human IL-1 β Biotin ref. 33-7110-68) for 1 h at rt. Plates were washed and incubated with HRP-streptavidin for 30 min at rt and washed again. The signal was developed after addition of 3,3',5,5'-tetramethylbenzidine-peroxidase (TMB) until colour appeared and the reaction was stopped by 2 M H₂SO₄. A microplate spectrophotometer (BioTek) was used to detect signals with 450 nm. The detection range of IL-1 β ELISA was 2-150 ng/mL.

[0476] **Protocol B.** PBMC were isolated from buffy coats by density gradient centrifugation on Histopaque-1077 (Sigma, cat no. 10771). Isolated cells were seeded into the wells (280,000 cells/well) of a 96-well plate and incubated for 3 h with lipopolysaccharide (LPS, 1 μ g/mL diluted 1000x from a 1 mg/mL stock solution). The compounds of the present disclosure were added (a single compound per well) and the cells were incubated for 30 min. Next, the cells were stimulated with ATP (5 mM final concentration diluted 20x from a 100 mM stock solution) for 1 h and the

cell culture media from the wells were collected for further analysis. The release of IL-1 β into the media was determined by quantitative detection of IL-1 β in the media using HTRF®, CisBio cat. No. 62HIL1BPEH. Briefly, cell culture supernatant were dispensed directly into the assay plate containing antibodies labelled with the HTRF® donor and acceptor. A microplate spectrophotometer (BMG) was used to detect signals at 655 nm and 620 nm. The detection range of IL-1 β HTRF® was 39-6500 pg/mL.

[0477] The determination of the IC₅₀ values was preformed using the Graph Pad Prism software and the measured IC₅₀ values of compounds of the present disclosure are shown in **Table A** below (“++++” means <0.1 μ M; “+++” means $\geq$ 0.1 and <1 μ M; “++” means $\geq$ 1 and <3 μ M; “+” means $\geq$ 3 and <10 μ M). These results show that the compounds of the present disclosure are capable of inhibiting IL-1 β release upon inflammasome activation.

Table A. Activity in PBMC Assay

Compound No.	Average PBMC IC ₅₀ (μ M)
1	++++
1A	++++
1B	++++
2A	++++
2B	+++
3A	++++
3B	++++
4	+++
5	+++
6	++++
7A	++++
7B	++++
8A	++++

[0478] **P-gp MDCK-MDR1 Studies.** The compounds of the present disclosure were tested in a MDCK-MDR1 permeability assay to assess whether they are actively transported out of cells by the efflux protein, P-glycoprotein (P-gp).

[0479] **Protocol.** MDCK-MDR1 cells were used between passage numbers 6-30. Cells were seeded onto Millipore Multiscreen Transwell plates at 3.4×10^5 cells/cm². The cells were cultured in DMEM and media was changed on Day 3. On Day 4 the P-gp inhibition study was performed. Cell culture and assay incubations were carried out at 37° C in an atmosphere of 5 % CO₂ with a relative humidity of 95 %. On the day of the assay, the monolayers were prepared by rinsing both

apical and basolateral surfaces twice with warmed (37° C) transport buffer (Hanks Balanced Salt Solution [HBSS] containing 25 mM HEPES and 4.45 mM glucose, pH 7.4). Cells were then incubated with transport buffer containing test compound or positive control inhibitor (elacridar) in both apical and basolateral compartments for 30 minutes at 37° C. The dosing solutions were prepared by diluting digoxin and test compound where applicable to give a final digoxin concentration of 5 µM (final DMSO concentration of 1 % v/v). The fluorescent integrity marker lucifer yellow was prepared in receiver solutions in vehicle or test compound-containing transport buffer. After pre-incubation, the transport buffer was removed from both apical and basolateral compartments and replaced with the appropriate dosing or receiver solution.

[0480] For assessment of B-A permeability, transport buffer was removed from the basolateral companion plate and replaced with dosing solution. Fresh transport buffer containing lucifer yellow and test compound where applicable (final DMSO concentration 1 % v/v) was added to the apical compartment insert, which was then placed into the companion plate. After a 90-minute incubation the apical compartment inserts and the companion plates were separated and compartments sampled for analysis. Seven concentrations of test compound (up to 100 µM) were assessed in addition to a vehicle control (0 µM). A triplicate determination of each concentration was performed. The positive control inhibitor was evaluated in parallel. [³H]-digoxin was quantified by liquid scintillation counting to give disintegrations per minute (dpm). The integrity of the monolayer throughout the experiment was checked by monitoring lucifer yellow permeation using fluorimetric analysis.

[0481] **BCRP and P-gp Caco-2 Studies.** The compounds of the present disclosure were tested in a Caco-2 permeability assay to assess whether they are actively transported out of cells by the efflux proteins, P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP).

[0482] **Protocol.**

[0483] Caco-2 cells were used between passage numbers 40-60. Cells were seeded onto Millipore Multiscreen Transwell plates at $\times 10^5$ cells/cm². The cells were cultured in DMEM and media was changed every two or three days. On Day 18-22 the BCRP inhibition study was performed. Cell culture and assay incubations were carried out at 37° C in an atmosphere of 5 % CO₂ with a relative humidity of 95 %. On the day of the assay, the monolayers were prepared by rinsing both apical and basolateral surfaces twice with warmed (37° C) transport buffer (Hanks Balanced Salt Solution [HBSS] containing 25 mM HEPES and 4.45 mM glucose, pH 7.4). Cells were then

incubated with transport buffer containing test compound or positive control inhibitor (novobiocin) in both apical and basolateral compartments for 30 minutes at 37° C. For the inhibition studies a P-gp inhibitor or BCRP inhibitor was included on both sides of the monolayer for the equilibration period. The dosing solutions were prepared by diluting estrone 3-sulfate and test compound where applicable to give a final estrone 3-sulfate concentration of 1 μ M (final DMSO concentration of 1 % v/v). The fluorescent integrity marker lucifer yellow was prepared in receiver solutions in vehicle or test compound-containing transport buffer. After pre-incubation, the transport buffer was removed from both apical and basolateral compartments and replaced with the appropriate dosing or receiver solution. For assessment of B-A permeability, transport buffer was removed from the basolateral companion plate and replaced with dosing solution. Fresh transport buffer containing lucifer yellow and test compound where applicable (final DMSO concentration 1 % v/v) was added to the apical compartment insert, which was then placed into the companion plate. After a 90-minute incubation the apical compartment inserts and the companion plates were separated and compartments sampled for analysis. Seven concentrations of compound (up to 100 μ M) were assessed in addition to a vehicle control (0 μ M). A triplicate determination of each concentration was performed. The positive control inhibitor was evaluated in parallel. [3 H]-estrone 3-sulfate was quantified by liquid scintillation counting to give disintegrations per minute (dpm). The integrity of the monolayer throughout the experiment was checked by monitoring lucifer yellow permeation using fluorimetric analysis. Corrected B-A apparent permeability (P_{app}) of probe substrate was calculated by subtracting its mean passive P_{app} determined in the presence of the highest concentration of positive control inhibitor (giving 100 % transporter inhibition). The mean corrected B-A P_{app} from vehicle wells (0 μ M test compound) was defined as 100 % transport activity and this value was then used to calculate the percentage control transport activity for all other test compound concentrations. Percentage control transport activity was plotted against test compound concentration and fitted to calculate an IC_{50} value.

[0484] **PAMPA Studies.** The compounds of the present disclosure were tested in a PAMPA permeability assay to assess passive transcellular permeation.

[0485] **Protocol.** 0.2 mM working solution was prepared by diluting 10 mM stock solution with DMSO. 10 μ M donor solution (5 % DMSO) was prepared by diluting 20 μ L of working solution with 380 μ L PBS. 150 μ L of 10 μ M donor solutions to each well of the donor plate, whose PVDF membrane was precoated with 5 μ L of 1 % lecithin/dodecane mixture. Duplicates were prepared.

300 μ L of PBS was added to each well of the PTFE acceptor plate. The donor plate and acceptor plate were combined and incubated for 4 hours at room temperature with shaking at 300 rpm. Preparation of T0 sample: 20 μ L donor solution was transferred to new well followed by the addition of 250 μ L PBS (DF: 13.5), 130 μ L ACN (containing internal standard) as T0 sample. Preparation of acceptor sample: The plate was removed from incubator. 270 μ L solution was transferred from each acceptor well and mixed with 130 μ L ACN (containing internal standard) as acceptor sample. Preparation of donor sample: 20 μ L solution was transferred from each donor well and mixed with 250 μ L PBS (DF: 13.5), 130 μ L ACN (containing internal standard) as donor sample. Acceptor samples and donor samples were all analysed by LC-MS/MS. The equation used to determine permeability rates (Pe) was displayed as follows: $VD = 0.15$ mL; $VA = 0.30$ mL; $Area = 0.28$ cm²; $time = 14400$ s; "[drug]acceptor = (Aa/Ai $\times$ DF)acceptor; [drug]donor= (Aa/Ai $\times$ DF)donor; Aa/Ai: Peak area ratio of analyte and internal standard; DF: Dilution factor."

[0486] **Thermodynamic Solubility Studies.** The compounds of the present disclosure were tested in an equilibrium solubility assay.

[0487] **Protocol**

[0488] An appropriate amount of test and control compounds were weighed into lower chambers of Whatman Mini-UniPrep vials. To these were added 50 mM pH 7.4 phosphate buffer (450 μ L) to get a super-saturated suspension. The samples were vortexed for at least 2 minutes. The Whatman Mini-UniPrep vials were shaken on a shaker for 24 hours at room temperature at 800 rpm. The vials were centrifuged for 20 minutes (eg. 4000 rpm). Samples were compressed to prepare filtrates for injection into HPLC system and the concentration calculated with a standard curve. **Table B** shows properties for selected compounds of the present disclosure. As shown in the table, compounds of the present disclosure may display improved properties (e.g., over the compounds in the prior art), such as enhanced potency, solubility, membrane permeability and transporter efflux.

[0489] The efflux ratio (ER) values of compounds of the present disclosure are shown in Table B below ("*****" means <3 ; "****" $3 \geq$ and <10 ; "***" means ≥ 10 and <30 ; "*" means ≥ 30).

[0490] The measured PAMPA permeability values of compounds of the present disclosure are shown in Table B below ("\$\$\$\$" means >10 nm / s; "\$\$\$" means ≥ 3 and <10 nm / s; "\$\$" means ≥ 1 and <3 nm / s; "\$" means <1 nm / s).

[0491] The measured thermodynamic solubility values of compounds of the present disclosure are shown in Table B below ($\phi \phi \phi \phi$ means ≥ 3 and < 10 mg/mL; " $\phi \phi \phi$ " means ≥ 1 and < 3 mg/mL; " $\phi \phi$ " means ≥ 0.3 and < 1 mg/mL; " ϕ " means < 0.3 mg/mL).

Table B

Compound No.	PAMPA Pe	Thermodynamic Solubility	MDCK-MDR1 ER	Caco-2 ER
1A	\$\$	$\phi \phi \phi \phi$		****
1B	\$\$	$\phi \phi \phi$		****
3A			*	
3B			*	
4	\$	$\phi \phi \phi$		**
5	\$\$	$\phi \phi \phi \phi$		***
6	\$\$\$\$	$\phi \phi \phi \phi$		****
7A	\$\$\$	$\phi \phi \phi \phi$	**	
7B	\$\$\$	$\phi \phi \phi \phi$	*	

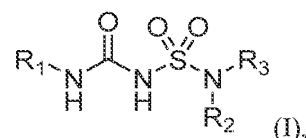
EQUIVALENTS

[0492] The details of one or more embodiments of the disclosure are set forth in the accompanying description above. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, the preferred methods and materials are now described. Other features, objects, and advantages of the disclosure will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms include plural referents unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents and publications cited in this specification are incorporated by reference.

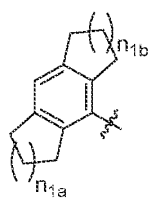
[0493] The foregoing description has been presented only for the purposes of illustration and is not intended to limit the disclosure to the precise form disclosed, but by the claims appended hereto.

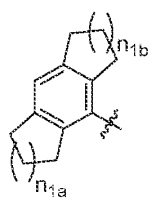
CLAIMS:

1. A compound of Formula (I):



or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein:



R_1 is , wherein n_{1a} and n_{1b} each independently are 0 or 1;

R_2 is $-(\text{CH}_2)_{n_2}\text{-R}_{2S}$, wherein n_2 is 1 or 2;

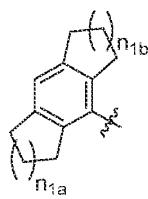
R_{2S} is 4- to 8-membered heterocycloalkyl in which at least one heteroatom is O, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with one or more R_{2SS} ;

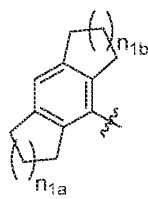
each R_{2SS} independently is $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ haloalkyl, halo, $-\text{CN}$, $-\text{OH}$, $-\text{O}(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{NH}_2$, $-\text{NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})_2$, or oxo;

R_3 is 5- or 6-membered heteroaryl optionally substituted with one or more R_{3S} ; and

each R_{3S} independently is halo, $\text{C}_1\text{-C}_6$ alkyl, or $\text{C}_1\text{-C}_6$ haloalkyl.

2. The compound of any one of the preceding claims, wherein:



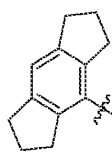
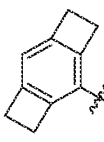
R_1 is , wherein n_{1a} and n_{1b} each independently are 0 or 1;

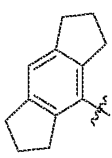
R_2 is $-(\text{CH}_2)_{n_2}\text{-R}_{2S}$, wherein n_2 is 1 or 2;

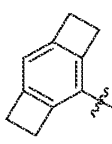
R_{2S} is 4- to 8-membered heterocycloalkyl in which at least one heteroatom is O, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with one or more $-\text{OH}$; and

R_3 is 5- or 6-membered heteroaryl optionally substituted with one or more $\text{C}_1\text{-C}_6$ alkyl.

3. The compound of any one of the preceding claims, wherein both of n_{1a} and n_{1b} are 1.

4. The compound of any one of the preceding claims, wherein R_1 is  or .

5. The compound of any one of the preceding claims, wherein R_1 is .

6. The compound of any one of the preceding claims, wherein R_1 is .

7. The compound of any one of the preceding claims, wherein R_2 is $-\text{CH}_2-\text{R}_{2s}$.

8. The compound of any one of the preceding claims, wherein R_2 is $-\text{CH}_2-\text{R}_{2s}$; and R_{2s} is tetrahydrofuranyl or tetrahydropyranyl, wherein the tetrahydrofuranyl or tetrahydropyranyl is optionally substituted with one or more $-\text{OH}$.

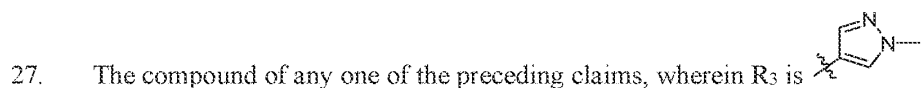
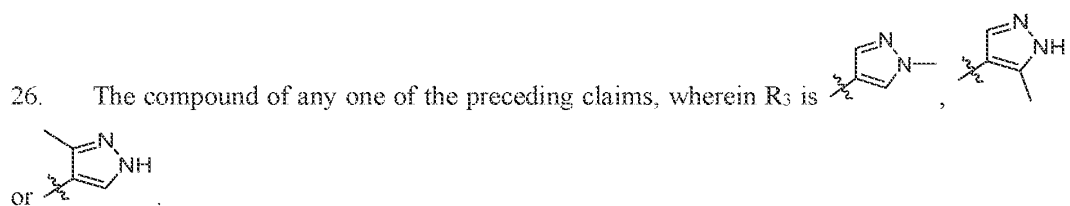
9. The compound of any one of the preceding claims, wherein R_2 is $-(\text{CH}_2)_2-\text{R}_{2s}$.

10. The compound of any one of the preceding claims, wherein R_2 is $-(\text{CH}_2)_2-\text{R}_{2s}$; and R_{2s} is tetrahydrofuranyl or tetrahydropyranyl, wherein the tetrahydrofuranyl or tetrahydropyranyl is optionally substituted with one or more $-\text{OH}$.

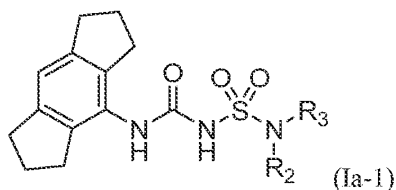
11. The compound of any one of the preceding claims, wherein R_{2s} is 5- to 6-membered heterocycloalkyl in which at least one heteroatom is O, wherein the 5- to 6-membered heterocycloalkyl is optionally substituted with one or more R_{2ss} .

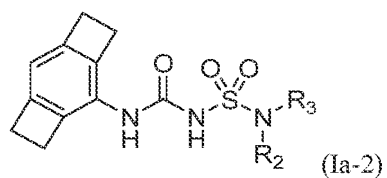
12. The compound of any one of the preceding claims, wherein R_{2s} is 5- to 6-membered heterocycloalkyl having one heteroatom, wherein the heteroatom is O, and wherein the 5- to 6-membered heterocycloalkyl is optionally substituted with one or more R_{2ss}.
13. The compound of any one of the preceding claims, wherein R_{2s} is 5-membered heterocycloalkyl having one heteroatom, wherein the heteroatom is O, and wherein the 5-membered heterocycloalkyl is optionally substituted with one or more R_{2ss}.
14. The compound of any one of the preceding claims, wherein R_{2s} is 6-membered heterocycloalkyl having one heteroatom, wherein the heteroatom is O, and wherein the 6-membered heterocycloalkyl is optionally substituted with one or more R_{2ss}.
15. The compound of any one of the preceding claims, wherein at least one R_{2ss} is -OH.
16. The compound of any one of the preceding claims, wherein R_{2s} is tetrahydrofuranyl or tetrahydropyranyl, wherein the tetrahydrofuranyl or tetrahydropyranyl is optionally substituted with one or more R_{2ss}.
17. The compound of any one of the preceding claims, wherein R_{2s} is tetrahydrofuranyl or tetrahydropyranyl, wherein the tetrahydrofuranyl or tetrahydropyranyl is optionally substituted with one or more -OH.
18. The compound of any one of the preceding claims, wherein R_{2s} is tetrahydrofuranyl optionally substituted with one or more -OH.
19. The compound of any one of the preceding claims, wherein R_{2s} is tetrahydrofuranyl.
20. The compound of any one of the preceding claims, wherein R_{2s} is tetrahydrofuranyl substituted with one or more -OH.

21. The compound of any one of the preceding claims, wherein R_{2s} is tetrahydropyranyl.
22. The compound of any one of the preceding claims, wherein R_{2s} is tetrahydropyranyl substituted with one or more -OH.
23. The compound of any one of the preceding claims, wherein R₃ is 5- or 6-membered heteroaryl substituted with one or more R_{3s}.
24. The compound of any one of the preceding claims, wherein R₃ is 5- or 6-membered heteroaryl substituted with one or more C₁-C₆ alkyl.
25. The compound of any one of the preceding claims, wherein R₃ is pyrazolyl substituted with one or more C₁-C₆ alkyl.



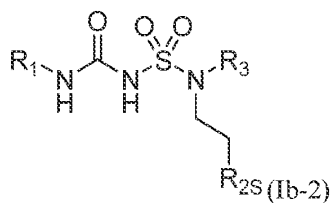
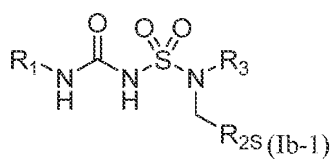
28. The compound of any one of the preceding claims, wherein the compound is of Formula (Ia-1) or (Ia-2):





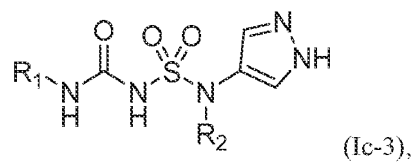
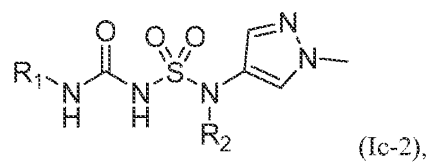
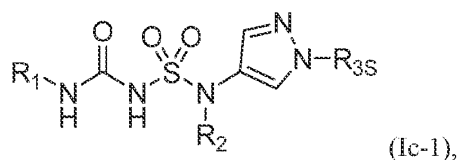
or a prodrug, solvate, or pharmaceutically acceptable salt thereof.

29. The compound of any one of the preceding claims, wherein the compound is of Formula (Ib-1) or (Ib-2):



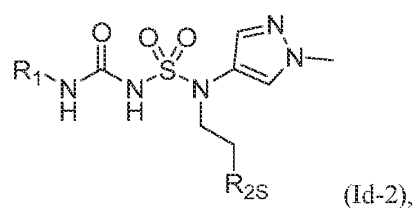
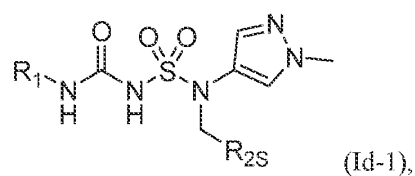
or a prodrug, solvate, or pharmaceutically acceptable salt thereof.

30. The compound of any one of the preceding claims, wherein the compound is of Formula (Ic-1), (Ic-2), or (Ic-3):



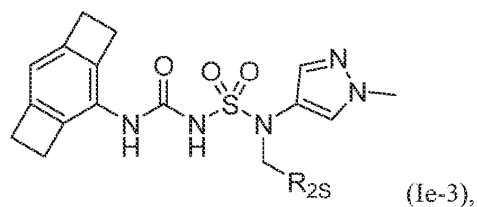
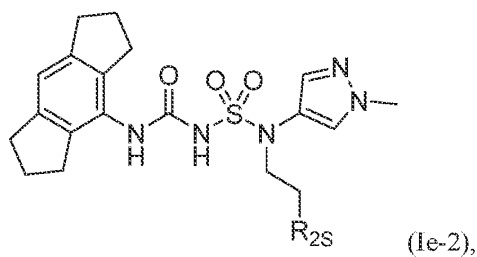
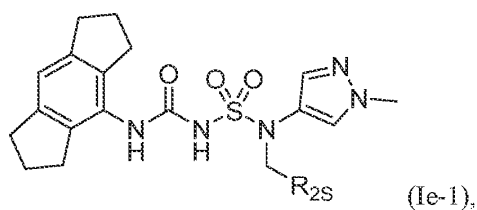
or a prodrug, solvate, or pharmaceutically acceptable salt thereof.

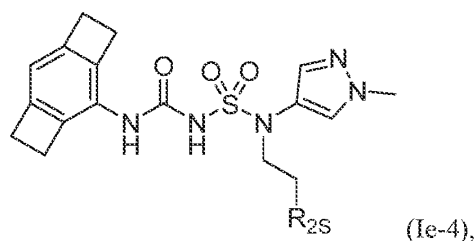
31. The compound of any one of the preceding claims, wherein the compound is of Formula (Id-1) or (Id-2):



or a prodrug, solvate, or pharmaceutically acceptable salt thereof.

32. The compound of any one of the preceding claims, wherein the compound is of Formula (Ie-1), (Ie-2), (Ie-3), or (Ie-4):





or a prodrug, solvate, or pharmaceutically acceptable salt thereof.

33. The compound of any one of the preceding claims, being selected from Compound Nos. 1, 1A, 1B, 2, 2A, 2B, 3, 3A, 3B, 4, 4A, 4B, 5, 5A, 5B, 6, 6A, 6B, 7A, 7B, 8A, and 8B, and prodrugs and pharmaceutically acceptable salts thereof.

34. A compound being an isotopic derivative of the compound of any one of the preceding claims.

35. A compound obtainable by, or obtained by, a method described herein;
optionally, the method comprises one or more steps described in Schemes 1-3.

36. An intermediate obtained by a method for preparing the compound of any one of the preceding claims;
optionally, the intermediate is selected from the intermediates described in Examples 1-12.

37. A pharmaceutical composition comprising the compound of any one of the preceding claims and a pharmaceutically acceptable diluent or carrier.

38. A method of inhibiting inflammasome activity, comprising contacting a cell with an effective amount of the compound of any one of the preceding claims; optionally, the inflammasome is NLRP3 inflammasome, and the activity is *in vitro* or *in vivo*.

39. A method of treating or preventing a disease or disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the compound of any one of the preceding claims, or the pharmaceutical composition of any one of the preceding claims.

40. The compound or pharmaceutical composition of anyone of the preceding claims, for use in inhibiting inflammasome activity; optionally, the inflammasome is NLRP3 inflammasome, and the activity is *in vitro* or *in vivo*.
41. The compound or pharmaceutical composition of anyone of the preceding claims, for use in treating or preventing a disease or disorder.
42. Use of the compound of any one of the preceding claims in the manufacture of a medicament for inhibiting inflammasome activity; optionally, the inflammasome is NLRP3 inflammasome, and the activity is *in vitro* or *in vivo*.
43. Use of the compound of any one of the preceding claims in the manufacture of a medicament for treating or preventing a disease or disorder.
44. The method, compound, pharmaceutical composition, or use of any one of the preceding claims, wherein the disease or disorder is associated with an implicated inflammasome activity; optionally, the disease or disorder is a disease or disorder in which inflammasome activity is implicated.
45. The method, compound, pharmaceutical composition, or use of any one of the preceding claims, wherein the disease or disorder is an inflammatory disorder, an autoinflammatory disorder, an autoimmune disorder, a neurodegenerative disease, or cancer.
46. The method, compound, pharmaceutical composition, or use of any one of the preceding claims, wherein the disease or disorder is an inflammatory disorder, an autoinflammatory disorder or an autoimmune disorder; optionally, the disease or disorder is selected from cryopyrin-associated auto-inflammatory syndrome (CAPS; *e.g.*, familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), chronic infantile neurological cutaneous and articular (CINCA) syndrome/ neonatal-onset multisystem inflammatory disease (NOMID)), familial Mediterranean fever (FMF), nonalcoholic fatty liver disease (NAFLD), non-alcoholic

steatohepatitis (NASH), gout, rheumatoid arthritis, osteoarthritis, Crohn's disease, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), fibrosis, obesity, type 2 diabetes, multiple sclerosis, dermatological disease (*e.g.*, acne) and neuroinflammation occurring in protein misfolding diseases (*e.g.*, Prion diseases).

47. The method, compound, pharmaceutical composition, or use of any one of the preceding claims, wherein disease or disorder is a neurodegenerative disease; optionally, the disease or disorder is Parkinson's disease or Alzheimer's disease.

48. The method, compound, pharmaceutical composition, or use of any one of the preceding claims, wherein the disease or disorder is cancer; optionally, the cancer is metastasising cancer, brain cancer, gastrointestinal cancer, skin cancer, non-small-cell lung carcinoma, head and neck squamous cell carcinoma or colorectal adenocarcinoma.

49. The method, compound, pharmaceutical composition, or use of any one of the preceding claims, wherein the disease or disorder is an inflammatory disease.

50. The method, compound, pharmaceutical composition, or use of any one of the preceding claims, wherein the inflammatory disease is associated with an infection.

51. The method, compound, pharmaceutical composition, or use of any one of the preceding claims, wherein the infection is a viral infection.

52. The method, compound, pharmaceutical composition, or use of any one of the preceding claims, wherein the viral infection is caused by a single stranded RNA virus.

53. The method, compound, pharmaceutical composition, or use of any one of the preceding claims, wherein the single stranded RNA virus is a coronavirus.

54. The method, compound, pharmaceutical composition, or use of any one of the preceding claims, wherein the coronavirus is Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV 2).
55. The method, compound, pharmaceutical composition, or use of any one of the preceding claims, wherein the inflammatory disease is associated with an infection by SARS-CoV 2 leading to 2019 novel coronavirus disease(COVID-19).
56. The method, compound, pharmaceutical composition or use of any one of the preceding claims, wherein the inflammatory disease comprises cytokine release syndrome (CRS).
57. The method, compound, pharmaceutical composition, or use of any one of the preceding claims, wherein the CRS is associated with COVID-19.
58. The method, compound, pharmaceutical composition, or use of any one of the preceding claims, wherein the CRS is associated with an adoptive cell therapy.
59. The method, compound, pharmaceutical composition, or use of any one of the preceding claims, wherein the adoptive cell therapy comprises chimeric antigen receptor T cell (CAR-T) therapy.